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UNRECOGNIZED GLUCOSE INTOLERANCE IS COMMON IN PULMONARY ARTERIAL HYPERTENSION

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Abstract

BACKGROUND—Animal and human data suggest insulin resistance is common in pulmonary arterial hypertension (PAH). Although routine assessment of insulin resistance is difficult, hemoglobin A1c (HbA1c) is a sensitive test to detect diabetes mellitus (DM) and those at high risk for diabetes. We aimed to define the prevalence of elevated HbA1c in PAH patients and to correlate HbA1c with functional assessment.

METHODS—HbA1c was measured in 41 PAH patients without a diagnosis of DM, along with demographic, functional, and hemodynamic data. Using published criteria, HbA1c ≤ 5.9% defined normal, 6.0–6.4% glucose intolerance, and ≥ 6.5% diabetes.

RESULTS—Twenty-three patients (56%) had HbA1c ≥ 6.0%, 6 patients (15%) had unrecognized DM (HbA1c ≥ 6.5%). Age and body mass index were similar in patients with HbA1c ≥ 6.0% versus HbA1c < 6.0%. There was a trend towards lower mean six-minute walk distance in patients with elevated HbA1c (331.0 ± 126.6 meters versus 413.6 ± 74.9 meters, p=0.07). Six-month event-free survival was not significantly different in patients with elevated HbA1c.

CONCLUSIONS—Unrecognized glucose intolerance as assessed by HbA1c is common in PAH. Further studies are needed to discern if glucose or insulin dysregulation mediates PAH pathogenesis or is secondary to advanced PAH.

Keywords

glucose intolerance; hemoglobin A1c; insulin resistance; pulmonary arterial hypertension; pulmonary hypertension

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Introduction

Pulmonary arterial hypertension (PAH) is a disease of the small pulmonary arteries, manifest by progressive vascular obliteration resulting in elevated pulmonary vascular resistance, right heart failure and death. PAH can be idiopathic, hereditary, or associated with a diverse group of disorders including connective tissue diseases, chronic liver disease and congenital heart disease [1]; thus the pathobiology of PAH is complex, involving multiple distinct pathways. There is no cure for PAH, and the morbidity and mortality remain substantial despite advances in therapy. This highlights the need for ongoing investigation into novel targets for disease modification and therapy.

Recent studies in humans and animal models point toward an association of abnormal insulin metabolism as well as other features of the metabolic syndrome (MS) with pulmonary vascular disease including PAH [2–7]. Mice deficient in peroxisome proliferator-activated receptor gamma (PPARγ) and apolipoprotein E (apoE) who are fed a high fat diet develop insulin resistance and pulmonary hypertension, reversed by PPARγ activation [7]. Adiponectin deficiency, strongly linked to obesity [8], insulin resistance and MS [9, 10], is another potential link between insulin resistance and PAH, and mice with adiponectin deficiency also develop pulmonary hypertension [2]. We have previously shown an association of MS with pulmonary venous hypertension in humans [3]. Insulin resistance was common in a retrospective cohort of female PAH patients using the triglyceride to high-density lipoprotein ratio [4], however insulin resistance and glucose intolerance have not been shown prospectively in PAH. Improved understanding of the importance and impact of insulin resistance and glucose intolerance, diabetes mellitus, and other metabolic derangements in PAH is needed.

Recently the American Diabetes Association Expert Committee has endorsed the use of hemoglobin A1c (HbA1c) in the diagnosis of diabetes mellitus (DM) [11]. While measurement of HbA1c does not quantitate insulin resistance, elevated HbA1c identifies patients with abnormal glucose metabolism at high risk for development of DM. An estimated 13% of US adults have glucose intolerance defined as HbA1c ≥ 6.0% [12]. Based on the potential relationship of insulin resistance and altered glucose metabolism in PAH, we hypothesized that glucose intolerance defined by HbA1c ≥ 6.0% would be common in outpatients with PAH and that glucose intolerance may be associated with worse functional status. We prospectively evaluated PAH patients in our outpatient practice and stratified them according to the presence or absence of glucose intolerance. Our finding that glucose intolerance is prevalent in PAH supports an association of insulin resistance and metabolic derangements in pulmonary vascular disease.

Materials and Methods

Study Design and Patient Population

Prospective new and returning clinic patients with pulmonary arterial hypertension (PAH) who presented for evaluation by pulmonary vascular disease specialists between March 1, 2009 and January 31, 2010 were eligible for inclusion. Patients with established DM or those receiving oral hypoglycemic agents or insulin therapy were excluded. Patients referred for any laboratory studies by their physician at the time of the clinic visit at our center were enrolled. Patients with World Health Organization Group I PAH were included, in accordance with published consensus guidelines [13]. Hemodynamic confirmation of PAH was established by right heart catheterization in all subjects and subjects were excluded if they had a pulmonary artery occlusion pressure > 15 mm Hg. Subjects were also excluded if they were diagnosed with pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, or portopulmonary hypertension. Patients taking more than 5 milligrams

per day of prednisone (or equivalent oral corticosteroid) were excluded. Patients with hemoglobinopathy, hemolytic anemia, thalassemia, and severe iron deficiency anemia were also excluded due to concerns for invalid results with HbA1c assay.

Detailed demographic, functional, and hemodynamic data were obtained and the medical record was reviewed for other relevant data including co-morbid disease, current medications, and survival outcomes (death, transplantation, addition of new PAH-specific therapy, hospitalization for right heart failure or exacerbation of PAH). Six-minute walk testing was performed according to American Thoracic Society consensus guidelines [14]. Data from right heart catheterization performed at our institution within three months of study entry were included in our analysis.

Whole blood was collected in EDTA tubes and glycosylated hemoglobin (HbA1c) was obtained using high performance liquid chromatography (HPLC) by standardized laboratory protocol using a method certified by the National Glycohemoglobin Standardization Program. Approval was obtained from the Vanderbilt University Institutional Review Board prior to data collection and analysis.

Definitions

Subjects were considered to have a prior history of diabetes mellitus (“known DM”) if there was a self-reported history of diabetes mellitus (DM), if their medical record contained the diagnosis of DM, or if they were receiving insulin, subcutaneous or oral hypoglycemic therapies. Patients who did not have any of the above criteria were defined as “no known DM”. Glucose intolerance, or highest risk for diabetes mellitus, was defined as HbA1c 6.0–6.4%, and frank diabetes as HbA1c ≥ 6.5% in accord with guidelines [11, 15]. We chose HbA1c ≥ 6.0% as a cutoff for glucose intolerance based on American Diabetes Association recommendations, as this is the value at which preventative interventions and intensive follow-up are suggested [11, 15, 16].

Features of MS were defined by the presence of hypertension, elevated triglycerides, reduced high-density lipoprotein cholesterol, and obesity in accordance with the International Diabetes and World Health Organization guidelines [17–19]. Hypertension was defined as treatment with antihypertensive medications, or recorded systolic BP ≥ 130 mm Hg, or diastolic BP ≥ 85 mm Hg. Elevated triglycerides or reduced high-density lipoprotein were identified by long-term use of statins, fibrates, or other lipid-lowering agents. Subjects with a body mass index (BMI) of ≥ 30 kg/m^2 were considered obese.

Statistical analysis

Continuous variables are expressed as mean ± SD values except as noted. Unpaired, two-tailed t-test and the Mann Whitney U-test were used to assess differences in continuous variables between groups according to specifications. Fisher’s exact or Chi-square tests were used to compare categorical variables. A multivariate linear regression model using BMI and HbA1c was utilized to examine effect on six-minute walk distance. Six-month event-free survival (defined as death, transplantation, hospitalization for right-heart failure or acute exacerbation of PAH, or addition of new vasodilator therapy) was evaluated using the Kaplan-Meier method and was compared using the log-rank test. Statistical analyses were performed using Prism 4.0 (Graph Pad Software Inc, La Jolla, CA) and SPSS Statistics Version 19 (IBM, USA). All P values are two-sided and a value < 0.05 was considered statistically significant.

Results

Clinical and hemodynamic characteristics of patients

Ninety-one new and returning patients with pulmonary arterial hypertension (PAH, including idiopathic PAH, heritable PAH and associated PAH) and no history of DM were evaluated at our center. Of these, 41 patients were enrolled and included in our analysis. Fifty patients were not enrolled due to exclusion criteria or because the treating physician did not order laboratory studies at the time of their visit. Baseline demographics, clinical and laboratory studies in PAH patients without established DM are shown in Table 1. The median HbA1c was 6.0% (interquartile range 5.7% to 6.3%). Among 41 PAH patients without known DM, 23 (56%) had HbA1c ≥ 6.0%. Six patients (14.6%) had HbA1c ≥ 6.5%, representing new diagnoses of DM. Patients with elevated HbA1c had similar age and type of PAH to those that had normal HbA1c (Table 1). The distribution of HbA1c in the cohort of PAH patients is shown in Figure 1. Mean CRP was higher in patients with elevated HbA1c, although this was not statistically significant (14.9 ± 16.1 mg/L versus 7.6 ± 12.3 mg/L, p = 0.06). Usage of low-dose maintenance oral corticosteroid for connective tissue disease was similar in the two groups (2 patients in HbA1c < 6.0% group, 4 patients in HbA1c ≥ 6.0% group). BMI was not different between groups (Table 1) and was not correlated with HbA1c (R^2 = 0.01, p = 0.79, Figure 2). The proportion of obese subjects (BMI ≥ 30 kg/m^2) was not different between groups (44.4% in HbA1c < 6.0% group, 39.1% in HbA1c ≥ 6.0% group, p = 0.76). No significant differences in hemodynamics between the two groups of patients were seen (Table 2).

Presence of features of MS

Features of the MS were common, however glucose intolerance was more common than any of the other features of MS (Table 3). Systemic hypertension was seen in 44% of our cohort. Obesity was seen in 41%, with a similar prevalence in patients with HbA1c < 6.0% and those with HbA1c ≥ 6.0% (p = 0.78). PAH patients with glucose intolerance more commonly had two or more features of the metabolic syndrome (43% versus 11%, p = 0.02), and four of the six PAH patients with incident DM had two or more features of MS.

Association of HbA1c with functional classification in PAH

Mean HbA1c in patients with WHO class I–II was 5.89% (95% CI 5.61 to 6.16) compared to 6.02% (95% CI 5.72 to 6.31%) in patients with WHO class III–IV symptoms (p = 0.06). Figure 3 shows the proportion of patients with HbA1c > 6.0% with mild (WHO class I–II) and moderate/severe (WHO class III–IV) symptoms. 13/19 (68%) of patients with WHO class III–IV symptoms had glucose intolerance compared to 10/22 (46%) of those with WHO class I–II symptoms (OR 1.51, 95% CI 0.9 to 2.6). Mean six-minute walk distance (6MWD, meters) was lower in the group of patients with elevated HbA1c, 331.0 ± 126.6 versus 413.6 ± 74.9 meters, p = 0.07 (Figure 4). Subjects with HbA1c > 6.0% walked on average 83 meters less than those with lower HbA1c (95% CI 3.4 to 161.7). Using a multivariate linear regression model, HbA1c ≥ 6.0% remained associated with lower 6MWD independent of BMI (p = 0.04).

Event-free survival analysis

Mean duration of follow up was similar for both groups: 8.8 months in the group with A1c < 6.0% versus 9.5 months in the group with A1c ≥ 6.0% (p = 0.34). PAH patients with HbA1c ≥ 6.0% had similar six-month event-free survival (Figure 5) as the group with HbA1c < 6.0% (p = 0.74).

Discussion

Emerging animal and human data suggest a relationship of insulin resistance with pulmonary arterial hypertension, offering new insights into PAH pathobiology and suggesting novel therapeutic targets. Our results show a high prevalence of HbA1c ≥ 6.0% in PAH and indicate a substantial portion of PAH patients are at high risk for development of diabetes mellitus (DM). In our study 56% of PAH patients without known DM had HbA1c ≥ 6.0% placing them at very high risk for development of DM, at a rate likely greater than ten times that of patients with lower HbA1c levels [11, 20–22]. Using the NHANES database, the estimated prevalence of HbA1c ≥ 6.0% in non-diabetic U.S. adults is 13% [12]. Thus our prevalence of 56% is much higher than the general population, suggesting that our results do not simply represent a report of a common population problem, but rather a potential relationship between elevated HbA1c and PAH. In addition, the mean HbA1c of 6.0 ± 0.6% in our cohort is significantly higher than recently reported population means of 5.5 ± 0.6% [23] and 5.29 (95% CI 5.28 – 5.31) [24] in non-diabetic Americans.

In our study, elevated HbA1c did not correlate with BMI, indicating that obesity alone was not driving glucose intolerance. The prevalence of other features of MS (hypertension, obesity, and dyslipidemia) was similar to previous studies [3]. The prevalence of glucose intolerance however, was higher than any single other MS risk factor, suggesting it may be the most critical feature of MS in PAH. Our results demonstrate that glucose intolerance in PAH is associated with worse functional capacity as assessed by 6MWD and suggest that HbA1c is more elevated in severe disease (WHO Class III–IV), although this was not statistically significant.

Whether abnormal glucose/insulin metabolism potentiates development of PAH, or simply is a marker of severe pulmonary vascular disease and/or heart failure is not clear. In this cross-sectional study we cannot establish cause-effect between glucose intolerance and PAH. We hypothesize that insulin resistance, characterized by elevations in circulating inflammatory cytokines, may contribute to direct endothelial cell injury [25, 26]. Deficiencies in apoE and PPARγ potentiate pulmonary hypertension in mice [2, 6], and may also play a role in development or exacerbation of pulmonary vascular disease in susceptible humans. Adipose tissue may represent another link: adiponectin and resistin, two adipokines dysregulated in insulin resistance, have been implicated in the development of pulmonary vascular injury [2] and myocardial dysfunction [2, 27, 28]. Insulin resistance is closely related to obesity and sedentary lifestyle [29, 30], thus decreased exercise and sedentary lifestyle in PAH may be another explanation for our findings. Insulin resistance and elevated HbA1c have been associated with incident systolic heart failure [31, 32], potentially related to changes in myocardial efficiency with a reliance on free-fatty acid metabolism, sympathetic activation, and direct myocyte injury [33–35]. Thus insulin resistance and glucose abnormalities in PAH may be related to failure of the right ventricle. Further study into these mechanisms in PAH and determination of whether treatment of insulin resistance ameliorates PAH is warranted.

Our study using HbA1c showed a similar prevalence of glucose intolerance (56%) as a prior retrospective analysis (45.7%) using a surrogate measure of insulin resistance, the triglyceride to high-density lipoprotein cholesterol ratio [4], suggesting the association is likely real. We used HbA1c, a direct measure of glycemia, to show that glucose intolerance in PAH is common and may be associated with poorer functional status. This is a novel observation in PAH, but is consistent with studies of insulin resistance and elevated HbA1c in systolic heart failure [36, 37]. We did not see a difference in event-free survival between HbA1c groups in our study. Possible explanations for this observation include the inclusion

of both incident and prevalent cases of PAH [38], the size of the study population, and the relatively short follow up period.

HbA1c is now widely accepted as a test to identify diabetes mellitus and patients at high risk for diabetes [11]. The HbA1c assay has many advantages for clinical use in PAH (no patient preparation or fasting required, clinician familiarity, ease and reproducibility of the assay, lack of significant biologic variability following stress or acute illness), however there are several limitations. The absolute cutoff of HbA1c corresponding to impaired glucose tolerance or impaired fasting glucose is still debated: values as low as 5.5–5.7% likely correspond to impaired glucose tolerance and an increased risk for development of DM [11, 21, 22], however guidelines suggest using a higher cutoff (6.0–6.4%) to detect those at highest risk. In accordance with guidelines [11], we chose a cutoff of 6.0% to select the highest risk group, however this may have underestimated the true prevalence of glucose intolerance in our cohort. HbA1c may not detect all glucose intolerant patients [12] and use of HbA1c may actually underestimate the burden of glucose intolerance and pre-diabetes.

The finding of a high prevalence of glucose intolerance in PAH highlights a need for heightened awareness of occult glucose intolerance in PAH, and perhaps a need to focus on risk factor modification for DM. Given the association of low physical activity and insulin resistance [29, 39], non-pharmacologic management with exercise programs, dietary education, and weight loss may gain more importance in management of pulmonary vascular disease. Structured exercise programs may improve 6MWD [40] and reduce HbA1c levels [41], thus implementation of structured exercise may be a particularly important intervention for PAH patients. None of the patients in our study were completing a structured exercise program, and thus differences in HbA1c values between groups are unlikely to be the result of formal exercise training alone.

Our study has several limitations. First, this is a single center study and our population may not reflect the PAH population in other centers. Despite this, the mean age, BMI, and distribution of PAH subclass and WHO functional classification were similar to other larger studies [4, 42]. While we did not observe a significant difference in mean BMI between groups, we did not measure waist circumference, thus we are unable to draw conclusions regarding the role of central obesity in our findings. This is a relatively small cohort of patients with a short duration of follow up, and this may account for the lack of statistically significant difference seen in event-free survival. The lack of a control population (with normal subjects or subjects with systolic heart failure) does not allow us to differentiate whether differences in glucose metabolism in PAH are different than in systolic heart failure. We enrolled only subjects referred for laboratory studies at our center, and selection of patients with more severe disease may be a confounder. As the prevalence of glucose intolerance and patient characteristics in our study were similar to other studies, we expect this effect was not significant [4, 42]. By including various etiologies of PAH we are unable to determine whether the finding of a high prevalence of glucose intolerance applies to all subtypes of PAH, as our small numbers preclude meaningful subgroup analysis. Strengths of the study include the prospective design, inclusion of all subtypes of PAH (similar to real-world practice), and ease of application of the intervention to clinical practice. Lastly, our results support the existing body of literature suggesting a relationship between insulin resistance and pulmonary arterial hypertension.

Many questions regarding the causal relationship of glucose intolerance and pulmonary vascular disease remain unanswered. This study provides evidence that should encourage clinicians to more carefully screen for glucose intolerance and DM in PAH patients. Future directions might include direct measurement and quantitation of insulin resistance in human

and mouse models of PAH, studies of the temporal relationship of insulin resistance to PAH, and trials of therapies to ameliorate insulin resistance in PAH.

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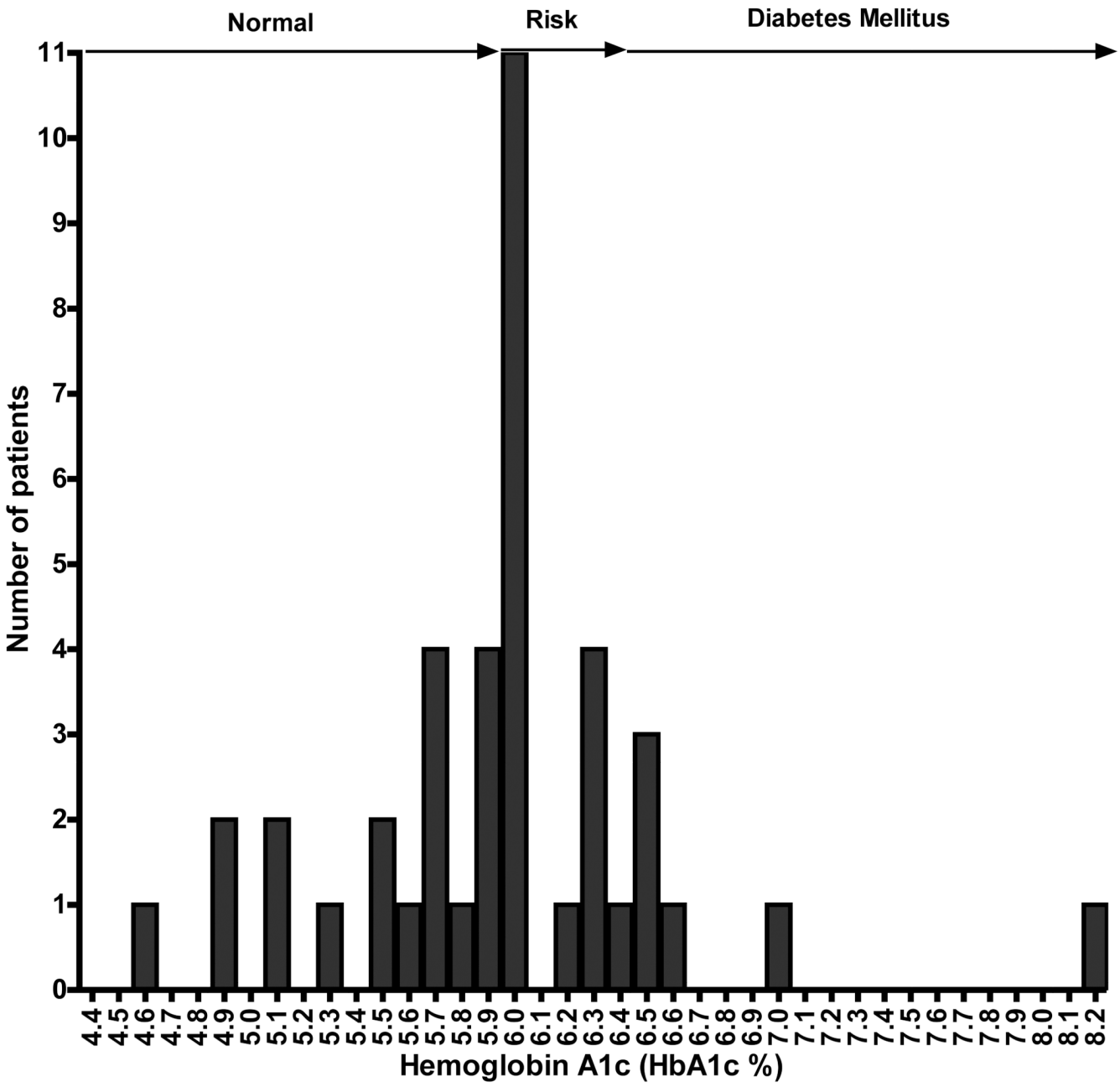

Figure 1. Distribution of Hemoglobin A1c (HbA1c) values in PAH patients without known history of Diabetes Mellitus (DM)

"No." represents the number of patients (total = 41) with each value of HbA1c. Arrows highlight HbA1c < 6.0% (normal), 6.0–6.4% (highest risk for development of DM, where further testing is indicated), and HbA1c ≥ 6.5% (cutoff for diagnosis of DM). Patients in shaded gray area represent those with high risk of DM or frank DM.

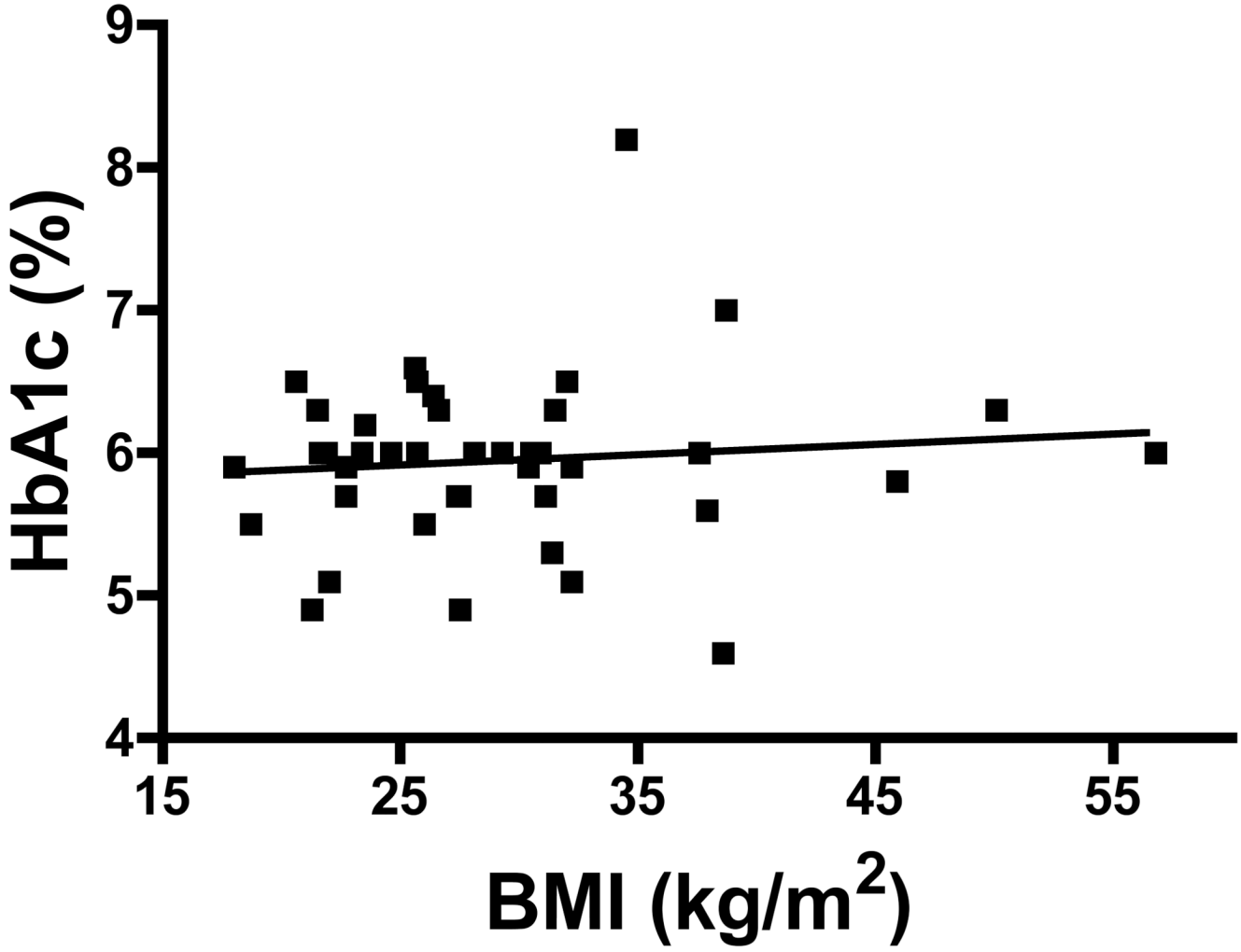

Figure 2. BMI is not correlated with HbA1c in PAH

Slope 0.007 (95% CI: −0.017 to 0.03), $R^2 = 0.01$, p = 0.79 using Spearman's correlation.

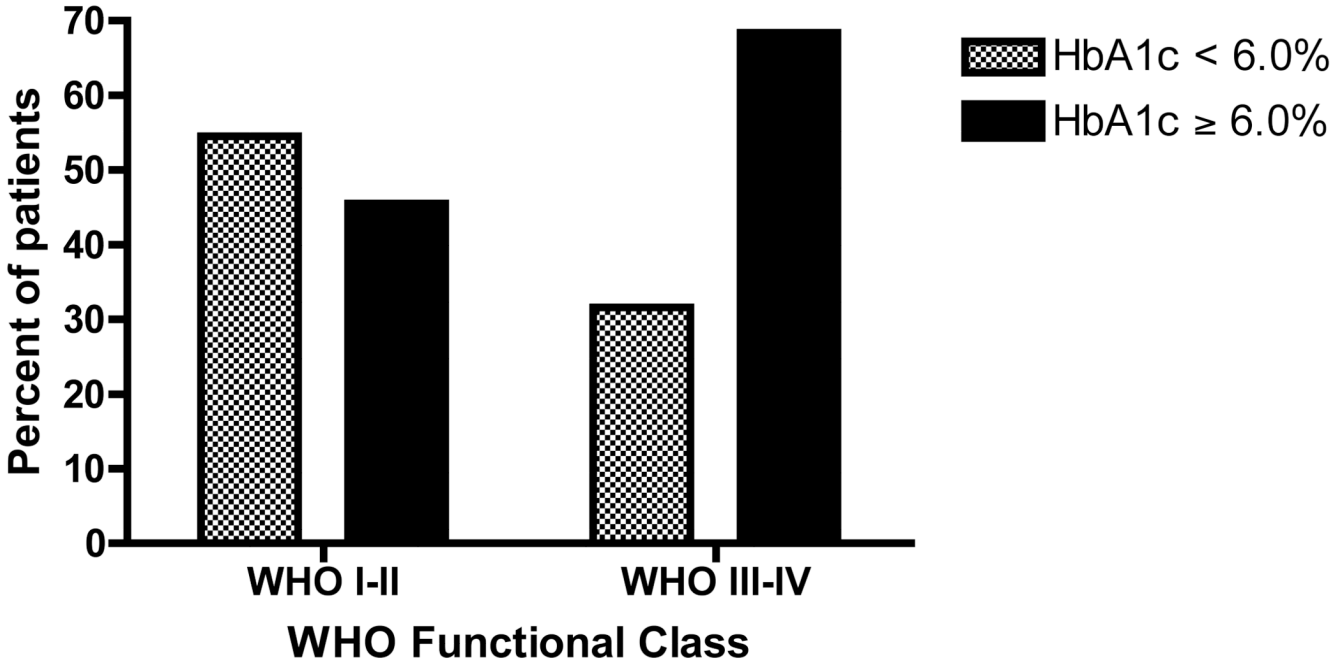

Figure 3. Glucose intolerance by WHO Class

HbA1c < 6.0% is shown grey bars, HbA1c ≥ 6.0% is show in solid black bars. P value = 0.14 between groups

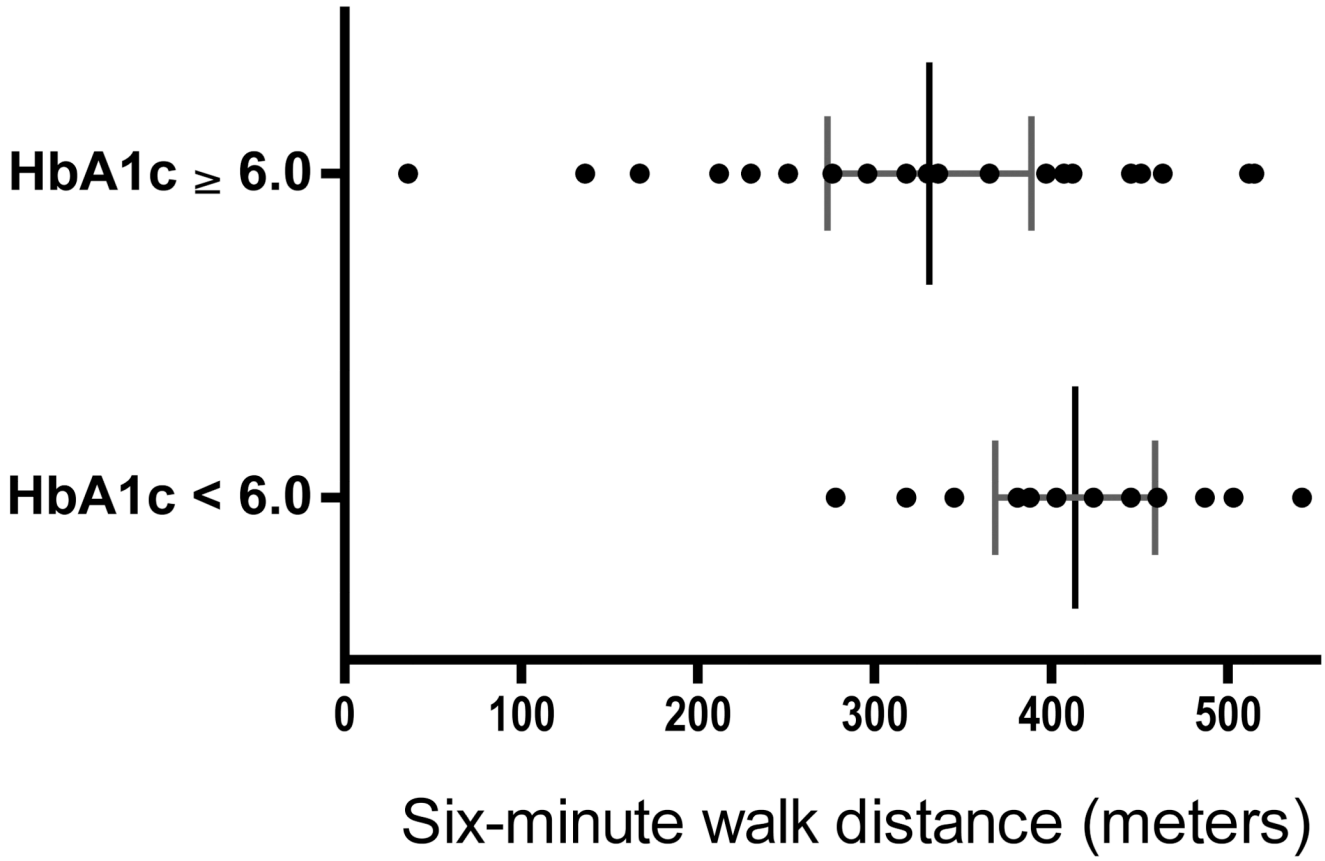

Figure 4. Mean six-minute walk distance is lower in patients with elevated hemoglobin A1c (HbA1c)

Dark bar demonstrates mean, grey bars represent 95% CI. *p value = 0.07 by Mann-Whitney U test.

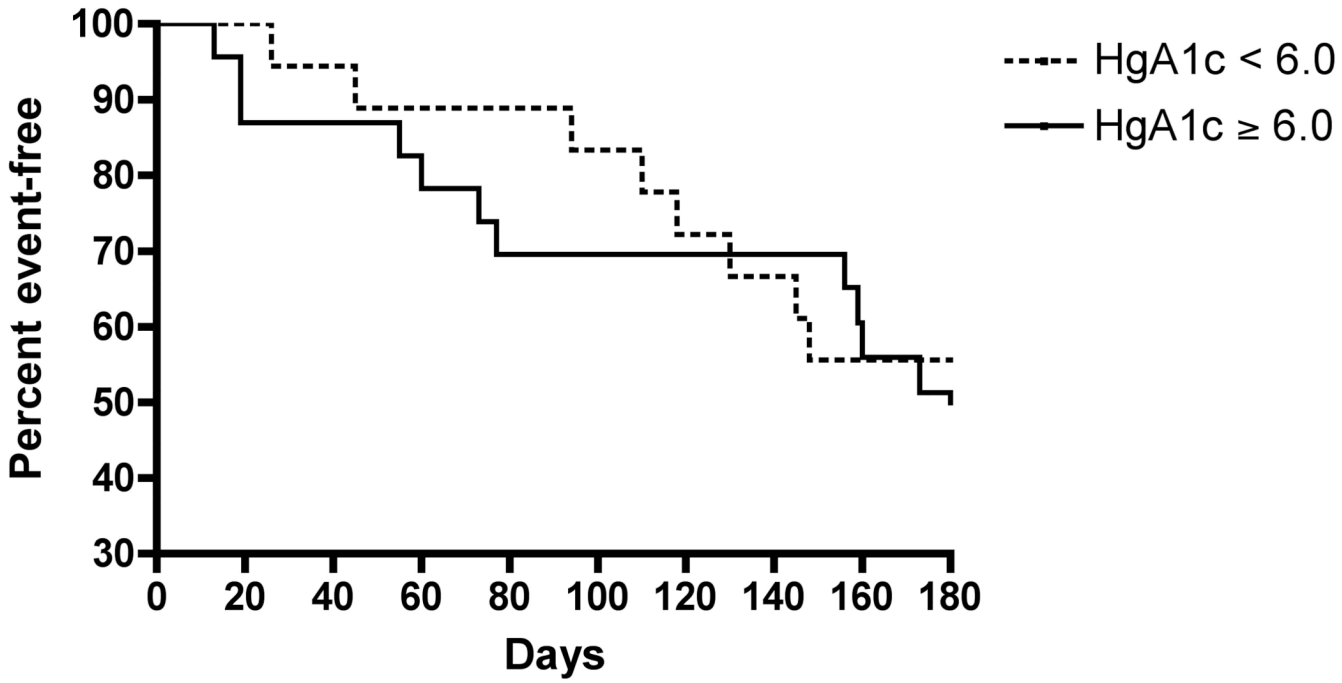

Figure 5. Kaplan-Meier six-month event-free survival curve in pulmonary arterial hypertension (PAH) by HbA1c

There was no significant difference in event free survival in PAH patients with HbA1c < 6.0% versus those with HbA1c ≥ 6.0% ($p = 0.74$). Events were defined as death, transplantation, hospitalization for right-heart failure or acute exacerbation of PAH, or addition of new PAH-specific therapy.

Table 1

Demographic and clinical characteristics of PAH patients

	All PAH	HbA1c < 6.0%	HbA1c ≥ 6.0%	P value*
Subjects, n (%)	41	18 (44)	23 (56)	
Type of PAH				0.55
IPAH/HPAH	26	13	13	
CTD	13	5	8	
CHD	1	0	1	
HIV	1	0	1	
Male sex, n	10	3	7	
Age (years)	52.3 ± 14	49.3 ± 18	54.6 ± 10	0.26
BMI (kg/m^2)	29.3 ± 8	28.5 ± 7	29.9 ± 9	0.90
CRP (mg/L)	11.4 ± 15	7.6 ± 12	14.9 ± 16	0.06
BNP (pg/mL)	450 ± 593	364 ± 616	525 ± 581	0.36
Systolic BP (mm Hg)	112.0 ± 20	112.4 ± 18	111.7 ± 21	0.74
Diastolic BP (mm Hg)	70.0 ± 9	70.3 ± 11	69.7 ± 8	0.98
Resting heart rate	85.0 ± 16	80.3 ± 11.2	88.7 ± 18.3	0.21
Resting oxygen saturation (%)	94.2 ± 3.4	95.4 ± 2.6	93.3 ± 3.8	0.10
PAH specific therapy, n				0.61
CCB monotherapy	2	1	1	
ERA monotherapy	7	3	4	
PDE-5 monotherapy	2	0	2	
Prost monotherapy	9	5	4	
Dual oral	6	2	4	
Oral + prostanoid	13	7	6	
None	2	0	2	
Echocardiographic data				
Left atrial size (cm)	3.77 ± 0.6	3.89 ± 0.6	3.69 ± 0.7	0.52
Left ventricular hypertrophy				0.47
None, n (%)	31 (76)	15 (83)	16 (70)	
Mild, n (%)	10 (24)	3 (17)	7 (30)	
Moderate/Severe, n (%)	0 (0)	0 (0)	0 (0)	
Relaxation abnormality				0.52
None, n (%)	33 (81)	14 (78)	19 (83)	
Mild, n (%)	7 (17)	3 (17)	4 (17)	
Moderate/Severe, n (%)	1 (2)	1 (6)	0 (0)	

Data are presented as mean ± SD and n (%) unless otherwise stated. Totals may not equal 100% due to rounding. PAH = pulmonary arterial hypertension. HbA1c = hemoglobin A1c. IPAH = idiopathic PAH. HPAH = heritable PAH. CTD = connective tissue disease associated PAH. CHD = congenital heart disease associated PAH. HIV = human immunodeficiency virus associated PAH. BMI = body mass index. CRP = C-reactive protein. BNP = brain natriuretic peptide. BP = noninvasive blood pressure. CCB = calcium channel blocker. ERA = endothelin receptor antagonist. PDE-5 = phosphodiesterase-5 inhibitor. Prost = prostanoid. Oral = oral therapy including PDE-5, ERA, or CCB.

*P values for difference between HbA1c < 6.0% and HbA1c ≥ 6.0% group using Mann-Whitney U, Fisher's exact test, or Chi-square per specifications.

Table 2

Hemodynamic characteristics of PAH patients

	HbA1c < 6.0%	HbA1c ≥ 6.0%	P value
RAP (mm Hg)	6.4 ± 4.4	8.4 ± 6.0	0.47
PA systolic (mm Hg)	84.8 ± 24.6	82.4 ± 18.2	0.97
PA diastolic (mm Hg)	34.9 ± 13.5	34.5 ± 9.5	0.73
mPAP (mm Hg)	53.9 ± 16.5	53.3 ± 7.9	0.81
PCWP (mm Hg)	8.5 ± 3.9	9.5 ± 5.9	0.85
CO (L/min)	4.7 ± 2.1	4.1 ± 1.1	0.66
CI (L/min/m^2)	2.6 ± 1.2	2.1 ± 0.5	0.46
PVR (woods units)	11.3 ± 6.1	10.2 ± 3.6	0.84
PA saturation (%)	67.0 ± 8.3	63.1 ± 6.7	0.20

Data are presented as mean ± SD except as noted. PAH = pulmonary arterial hypertension. RAP = right atrial pressure, PA = pulmonary artery, mPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, CO = cardiac output (Fick), CI = cardiac index (Fick), PVR = pulmonary vascular resistance. P values based on Mann-Whitney U test.

Table 3

Features of the Metabolic Syndrome (MS) in PAH.

	All PAH	HbA1c < 6.0	HbA1c ≥ 6.0%	P value[##]
Subjects, n (%)	41	18	23	
Hypertension	18 (44)	5 (28)	13 (57)	0.07
Dyslipidemia[#]	7 (17)	1 (6)	6 (26)	0.09
Obesity	17 (41)	8 (44)	9 (39)	0.78
HbA1c ≥ 6.0%	23 (56)			
2 features MS	12 (29)	2 (11)	10 (43)	0.02

PAH = pulmonary arterial hypertension. HbA1c = hemoglobin A1c.

[#]Dyslipidemia includes history of elevated triglycerides, low high-density lipoprotein cholesterol as defined by guidelines [19] or medical therapy for dyslipidemia. Values in percent have been rounded to nearest percent.

[##]P value calculated using Chi Square or Fisher's exact test.