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HbA_{1c} in pulmonary arterial hypertension: A marker of prognostic relevance?

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BACKGROUND: Patients with pulmonary arterial hypertension (PAH) exhibit impaired glucose metabolism and increased insulin resistance. The clinical consequences of these metabolic changes are not known.

METHODS: We assessed HbA_{1c} levels in 115 patients newly diagnosed with PAH (79 females and 36 males; mean age 49.2 years; idiopathic $n = 67$, collagen vascular disease $n = 16$, congenital heart defect $n = 19$, pulmonary veno-occlusive disease $n = 8$, portopulmonary $n = 5$). No patients had diabetes or were receiving anti-diabetic medication or systemic steroids. After initiation of pulmonary vasoactive treatment, patients remained in long-term follow-up.

RESULTS: Initially, patients were in an advanced stage of disease (mean pulmonary arterial pressure 53 ± 18 mm Hg, cardiac index 2.3 ± 0.8 liters/min/m^2) with a 6-minute-walk distance of 337 ± 123 meters, and in NYHA Functional Class 3.0 ± 0.7. The HbA_{1c} was $5.73 \pm 0.75\%$. A moderate but statistically significant positive correlation was observed between HbA_{1c} levels and BNP ($r_p = 0.41$, $p = 0.014$), but no correlation was found with hemodynamics or 6-minute-walk distance. The 5-year survival rate for the entire group was 68%. Kaplan–Meier analysis and multivariate Cox proportional hazard models correcting for demographic and clinical covariates revealed that patients with HbA_{1c} <5.7% had a significantly better 5-year survival compared with those having higher initial values (85.1% vs 55.9%; log rank $p = 0.002$). HbA_{1c} was a predictor of all-cause mortality with a hazard ratio of 2.23 (95% CI 1.06 to 4.70; $p = 0.034$) per 1-unit increase of HbA_{1c}.

CONCLUSIONS: In patients with pulmonary arterial hypertension, the HbA_{1c} level at time of diagnosis is an independent predictor of long-term prognosis.

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Pulmonary arterial hypertension (PAH) is a chronic pulmonary vascular disease characterized by progressive pulmonary vascular remodeling leading to right ventricular dysfunction and right heart failure. PAH encompasses several forms of the disease, including idiopathic PAH and PAH due to collagen vascular disease, congenital heart disease and portopulmonary hypertension.[1] All these forms of PAH are characterized by similar histologic features, including intimal and medial hypertrophy and plexiform lesions. In severe pulmonary hypertension, atherosclerotic lesions might also be present.[2]

In recent years, PAH has been recognized as a disorder with pronounced systemic and metabolic consequences, including systemic hypotension, renal impairment, hyperuricemia, hyponatremia and hypocapnia.[3–6]

Impaired glucose metabolism has been noted in pulmonary hypertension. The loss-of-function mutations in bone morpho-

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genetic protein receptor 2 (BMPR2) associated with the development of PAH may affect downstream targets of BMPR2 signaling, such as peroxisome proliferator–activated receptor gamma (PPARγ) and apolipoprotein E (apoE). Both PPARγ and apoE are involved in glucose metabolism. Animal studies have demonstrated that insulin resistance in apoE-deficient mice and deficiency of PPARγ in smooth muscle cells of transgenic mice lead to the development of a mouse pulmonary hypertension phenotype.[7–11]

In female PAH patients, insulin resistance appears to be more common than in the general population and has been associated with worse short-term survival.[12]

Increased glucose intolerance—assessed by the concentration of glycosylated hemoglobin A_{1c} (HbA_{1c})—has been noted in patients with PAH, but without effect on 6-month event-free survival.[13]

In the present study, we assessed HbA_{1c} concentrations in patients newly diagnosed with PAH prior to commencement of therapy and correlated HbA_{1c} values with the long-term survival of these patients.

Methods

At the Giessen Pulmonary Hypertension Center (Department of Internal Medicine, University Hospital Giessen, Germany), a specialized referral center, patients with pulmonary hypertension (PH) were diagnosed and evaluated with respect to the underlying disease. Diagnosis of PAH was made according to current recommendations[1] by means of clinical examination, transthoracic echocardiography, pulmonary function tests, cardiopulmonary exercise testing, blood-gas analyses, screening for human immunodeficiency virus (HIV) and collagen vascular diseases, coronary angiography or sleep studies, as clinically indicated. The presence of chronic thromboembolic pulmonary hypertension or parenchymal lung disease was excluded using thoracic computed tomography, computed tomographic pulmonary angiography and pulmonary perfusion scintigraphy. The diagnosis of pre-capillary PH was confirmed on initial right heart catheter investigation based on a mean pulmonary arterial pressure (mPAP) of >25 mm Hg, a pulmonary arterial wedge pressure (PAWP) of <15 mm Hg and a pulmonary vascular resistance (PVR) of >240 dyn/s/cm^5. The presence of right-to-left shunting had been excluded by transthoracic contrast echocardiography and standardized contrast-enhanced transcranial Doppler sonography.[14]

In addition to routine laboratory values, brain natriuretic peptide (BNP), fasting blood glucose levels and HbA_{1c} levels (Dimension Vista HbA1c Kit; Siemens Healthcare, Erlangen, Germany) were assessed. After diagnosis of PAH, patients were started on pulmonary vasoactive treatment with either endothelin receptor blockers, phosphodiesterase-5 inhibitors or prostanoids. When indicated, treatment with calcium channel blockers was initiated. In addition, patients were started on oral anti-coagulation if not contraindicated.

Patients were further assessed by World Health Organization (WHO) functional classification, 6-minute-walk distance (6MWD) and, if indicated, pulmonary hemodynamics, according to current guidelines.[1] HbA_{1c} levels were assessed with respect to clinical, functional and hemodynamic parameters at the time of presentation. Furthermore, long-term follow-up was undertaken, paying particular attention to survival while on pulmonary vasoactive treatment with respect to initial HbA_{1c} levels.

Clinical stabilization on initial treatment was assessed by measuring time to clinical worsening (TTCW), which has been defined by including time from start of specific medication to the beginning of an additional pulmonary vasoactive treatment compound or all-cause death. The decision of initiation of combination therapy has been based on criteria as outlined in the current PAH guideline.[1]

Follow-up data were retrieved from the local PAH database, review of patient histories and correspondence, or via telephone contact to the patient or family doctor, respectively.

Statistical analysis

Because the data exhibited a normal distribution, parameters are displayed as mean ± standard deviation, otherwise median ± interquartile range data are presented. To test for significant differences between groups, a 2-tailed Student's *t*-test was used. Correlations between 2 variables were analyzed using Pearson's correlation coefficient. Analysis of variance (ANOVA) was used to identify relevant covariates for survival.

Kaplan–Meier analyses with log-rank test and multivariate Cox proportional hazard models correcting for demographic and clinical covariates were used to assess the difference in survival depending on the level of HbA_{1c} at time of initial assessment.

Uni- and multivariate Cox regression models were used to calculate hazard ratios and a multivariate survival analysis (also using Cox's regression mode) was used to eliminate significant covariates and to assess independent predictors for long-term-survival. $p < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS, version 17.0 (SPSS, Inc., Chicago, IL).

Patients gave written informed consent for entering the study. The study has been approved by the ethics committee of the Medical Division of the Justus Liebig University of Giessen (Approval No. 113/11).

Results

Characteristics of PAH patients

Between June 1996 and July 2007, 529 patients were diagnosed with PAH at our center. Exclusion criteria for this study were: corticosteroid treatment ($n = 42$); a diagnosis of diabetes mellitus according to the new guidelines ($n = 53$)[15]; previous treatment with pulmonary vasoactive compounds ($n = 27$); lack of an available HbA_{1c} measurement at time of initial presentation ($n = 194$) or lack of follow-up data ($n = 98$). Survival data were collected until May 2010.

Subsequently, 115 therapy-naive patients newly diagnosed with PAH were included in the analysis, among them 79 women and 36 men, with a mean age of 49.2 years and a mean HbA_{1c} of 5.73 ± 0.75% prior to commencement of pulmonary vasoactive treatment. The demographic, hemodynamic, clinical and laboratory characteristics of the study subjects are summarized in Table 1. Baseline criteria of the patients ex-