REGULAR ARTICLE

Metabolic Disorders of Pulmonary Hypertension

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There is overlap between pulmonary hypertension and metabolic disorders. According to the 6th World Symposium on Pulmonary Hypertension, glycogen storage diseases and Gaucher disease are included in the heterogeneous group 5 pulmonary hypertension. This review highlights the known insights into the role of metabolic disorders and pulmonary hypertension, including epidemiology, pathogenesis, diagnosis, and treatment of pulmonary hypertension. Thyroid disorders have multiple mechanisms by which association with pulmonary hypertension have been described, and these will also be discussed. Pulmonary hypertension-specific targeted therapies and disease-specific therapies have been suggested, and the use alone or in combination has variable responses.

INTRODUCTION

The 6th World Symposium on Pulmonary Hypertension proposed to include pulmonary vascular resistance ≥3 Wood Units in the definition of all forms of precapillary pulmonary hypertension (PH) associated with mean pulmonary artery pressure >20 mmHg.[1] Since 1998, group 5 has undergone significant changes from "disorders directly affecting the pulmonary vasculature" to "miscellaneous" in 2003, until more recent updates wherein multiple pathophysiological processes are included in this group.

As part of this heterogenous group, metabolic disorders have been recognized to play a role in predominant pathophysiological mechanisms related to PH. Those include glycogen storage disease and Gaucher disease. Thyroid disorders, while not specifically included in the World Symposium classification, have multiple mechanisms by which PH association have been described, and thus will also be discussed in this review. We will describe the epidemiology, pathogenesis, and management of these metabolic associations of PH (Table 1).

Table 1. Epidemiology, Associations, and Management of Metabolic Disorders of PH

	Glycogen storage disease	Lysosomal storage disease
Prevalence of PH	25% in glycogen storage disease type 1	30% if Gaucher disease is untreated and 7% if the disorder is treated
Portocaval shunt	Yes	Yes
Splenectomy	No	Yes
Genetic association with PH risk	No	Yes
Screening of PH by echocardiogram recommended	Yes	Yes
PH specific therapy	Limited experience	Limited experience

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GLYCOGEN STORAGE DISEASE

Glycogen storage diseases are caused by genetic alterations of the glycogen metabolism leading to deposition of glycogen various organs, predominantly liver and kidney. There are 11 different types of glycogen storage disease, varying by enzyme deficiency and clinical manifestations. There are PH case reports related to glycogen storage disease type 1 (von Gierke disease) and 2 (Pompe disease). Among the varieties of glycogen storage disease, PH has predominantly been described in glycogen storage disease type 1.

Glycogen Storage Disease Type 1

In glycogen storage disease type 1, there is deficiency of the glucose 6-phosphatase enzyme (GSD 1a) or a deficiency in the microsomal transport proteins for glucose 6-phosphate (GSD 1b). This condition is usually diagnosed during infancy with hypoglycemia between feedings. About 25% of the patients with glycogen storage disease are thought to have type 1. The incidence of

Table 2. Reported Cases of Pulmonary Hypertension With Patients With Glycogen Storage Disease Type I

Author	GSD	Age of PH diagnosis (year)	Sex	Portocaval shunt	Pathology	Survival
Pizzo[5]	1	16	F	Yes	Intimal fibrosis, medial hypertrophy, plexiform lesions	No
Hamaoka[7]	1	12	F	No	Fibrous occlusion, plexiform lesions	No
	1	16	M	Yes	N/A	No
Ohura[8]	1	21	F	No	N/A	No
Bolz[9]	1	4	F	No	Intimal fibrosis	No
Kishnani[4]	1	24	F	No	N/A	No
Humbert[3]	1	25	M	Yes	N/A	No
Ueno[10]	1	17	M	No	N/A	Yes
Torok[11]	1	14	M	No	N/A	Yes

glycogen storage disease type 1a is 1 per 100 000.[2] To date, the incidence of PH is unknown in glycogen storage disease, and only 11 patients with glycogen storage disease 1 have been reported with PH (Table 2).[3-11] Of these, 5 had associated conditions that could also precipitate PH, including portocaval shunts, atrial septal defect, and hereditary hemorrhagic telangiectasia.

Some have hypothesized that patients with PH related to glycogen storage disease type 1 have similar characteristics to 6th World Symposium Group 1 PH (pulmonary arterial hypertension) because they have elevated serotonin levels, a vasoconstrictive amine that serves as pulmonary vasoconstrictor and growth factor for vascular smooth muscle cells stored in platelets.[2] Based on this hypothesis, Humbert et al[12] collected plasma serotonin in 13 patients with glycogen storage disease 1a, 1 patient with severe PH and glycogen storage disease 1a, and 16 patients with severe PH. Interestingly, plasma serotonin was dramatically elevated in the patient with glycogen storage disease 1a and PH (113.4 nmol/L), compared to cases with only severe PH (38.8 ± 7.3 nmol/L) or glycogen storage disease 1a (36.8 ± 11.5 nmol/L). This finding prompted the consideration for PH targeted therapy in this population. Ueno and colleagues[10] used sildenafil in a 17-year-old patient who developed syncope, was diagnosed low cardiac output right sided heart failure, and had improvement of hemodynamics and biomarkers after 3 weeks on single therapy treatment.

Screening for PH by periodic echocardiography has been suggested in these groups. The known reported cases of glycogen storage disease type 1 and PH were in children older than 10 years of age. Hence, screening can be timed and planned accordingly according to guidelines for glycogen storage disease for patients 10 years of age and older.[2,13]

Glycogen Storage Disease Type 2

Li and colleagues[14] described one case of PH with glycogen storage disease type 2 in a 16-year-old girl with severe respiratory muscle weakness, leading to impaired pulmonary function and respiratory failure. She was found to have PA systolic pressure 65 mm Hg and chronic respiratory acidosis with pH 7.3 and Pco_2 83 mm Hg. They speculated that severe muscle weakness leading to impaired pulmonary function and respiratory failure may have precipitated PH. Our group has previously described mechanisms by which hypercarbia can also directly contribute to pulmonary vasoconstriction and vascular remodeling, including via increased hydrogen ion concentration and sympathetic nervous systemic activation.[15]

LYSOSOMAL STORAGE DISORDER (GAUCHER DISEASE)

Gaucher disease is an autosomal recessive inherited disorder characterized by lysosomal storage disease in which there is a deficiency of the enzyme glucocerebrosidase. Consequently, there is glucocerebroside accumulation in the macrophage-monocyte system and organ infiltration, predominantly in the bone marrow, liver, and spleen. The adult or chronic form (type 1) comprises the majority of cases of Gaucher disease, compared to the less common infantile or acute form (type 2) (Table 3).

Table 3. Gaucher Disease

Gaucher disease	Type 1	Type 2	Type 3
Age at onset	Childhood or adulthood	Infancy	Childhood or adolescence
Pulmonary hypertension	Yes	Yes	Yes
Hepatosplenomegaly	Yes	Yes	Yes
Bone disease	Yes	No	Yes
Neurodegeneration	No	Yes	Yes
Age at death	Childhood or adulthood	Median 9 months	Childhood or early adulthood
Ethnic origin	Pan-ethnic or Ashkenazi Jews	Pan-ethnic	Pan-ethnic or Norrbottnian type from Sweden

The proposed mechanism of PH in Gaucher disease is accentuated basilar deposition of glucocerebroside in the interstitium (demonstrated as septal thickening), along with vasculopathy due to pulmonary alveolar capillary occlusions and fatal bone marrow microemboli.[16-18] Gaucher cells have been identified in the pulmonary parenchyma, intracapillary beds, patchy infiltrates in the lymphatic distribution, intra-alveolar infiltrates, and interstitial space (peri-bronchial, perivascular and septum).[18] The universal involvement of the pulmonary capillaries suggests the systemic nature of the disease. Interestingly, however, Gaucher disease type 1 has been associated with isolated PH, without Gaucher cells in the lung parenchyma.

Gaucher disease has indirect mechanisms by which it also contributes toward pulmonary vascular disease, as it is also associated with splenectomy and liver disease, both of which contribute to the development of PH. After splenectomy, thromboembolism may occur secondary to bone marrow infarction and enforcement of capillaries by megakaryocytes from extramedullary hematopoiesis. Furthermore, the presence of splenectomy in Gaucher disease is strongly associated with severe and life-threatening PH; in a study by Mistry et al[19] all patients with severe PH (right ventricular systolic pressure 50-130 mm Hg) were asplenic compared to only 31% of patients with right ventricular systolic pressure <50 mm Hg (odds ratio 28.8, 95% confidence interval 1.6-531.6, $P < .001$). Removal of the spleen, the primary reservoir of cell storage, will promote migration of mononuclear phagocytes toward other tissues, such as liver, skeletal muscle, and lung. Hence, there is perpetual remodeling of the vascular wall. Genetic associations of BMPR2 and ALK1 have not shown to be modifiers in Gaucher disease type 1.[20] Liver involvement is common in Gaucher disease, with its severity and clinical significance spanning a wide spectrum ranging from asymptomatic to cirrhosis. Portal hypertension can lead to pulmonary artery hypertension, while hyperdynamic circulation commonly seen in cirrhosis physiology can cause PH due to high increased right ventricular cardiac output.

The incidence of PH in untreated Gaucher disease type 1 is 30%, and it can be reduced to 7% in cases receiving enzyme replacement therapy.[19] Individuals can develop PH on the basis of elevated pulmonary vascular resistance and hepatopulmonary syndrome. Elstein et al[21] studied 134 adults with Gaucher disease type 1, and since 7% of the cases had PH, they recommended routine echocardiographic monitoring of all treated and untreated patients with enzyme replacement therapy. Risk factors for developing PH include female sex, splenectomy, angiotensin converting enzyme 1 gene polymorphism, acid beta-glucosidase gene mutation, poor compliance with enzyme replacement therapy, and positive family history (ie, sibling with Gaucher disease and PH).[19,20] The severity of Gaucher disease does not correlate with severity of PH.[22] Similar to the risk factors for developing PH, specific mutations (ie, non-N370S mutation of GBA gene), positive family history of similar phenotype, ACE 1 allele), and epigenetic modifiers such as female sex or a history of splenectomy predict severity of PH.

Enzyme replacement therapy is proven to be safe and effective in the treatment of Gaucher disease type 1, establishing imiglucerase as the current standard of care. In PH patients with Gaucher disease, the use of enzyme replacement therapy and use of PH-targeted therapy has been described.[16,19] The literature has few cases of Gaucher disease type 1 patients requiring lung transplant related to PH and parenchymal lung disease, all of them female with prior splenectomy. The first case with Gaucher disease type 1 that underwent lung transplant was a 10-year-old patient with extensive interstitial lung disease, with Gaucher cells by bronchoalveolar lavage.[23] Later on, Goobie and et al[24] and de Boer et al[25] described 2 cases of female patients with Gaucher disease type 1 with severe PH and splenectomy treated with enzyme replacement therapy with imiglucerase and PH-targeted therapy with bosentan, sildenafil, and epoprostenol. The patients underwent bilateral lung transplant, and the explanted lungs showed pulmonary vascular finding consistent with pulmonary artery hypertension, without Gaucher cells. The lack of Gaucher cells was thought to be related to the use of imiglucerase in the pretransplant period. On the contrary, other authors have shown possible, albeit slight, worsening of PH with the use of enzyme replacement therapy. Goitein et al[26] described their experience of symptomatic lung involvement in 8 patients with Gaucher disease who presented with prominent pulmonary symptoms, and from that cohort 2 adults treated with enzyme replacement therapy demonstrated new or worsening PH on the basis of Doppler estimated pressure on echocardiogram. The clinical significance of this is unknown, and likely minimal, as the increases in estimated pulmonary artery systolic pressure reported was not clear and seemingly ranged from approximately 5 mm Hg to 10 mm Hg. High resolution computed tomography and chest x-ray showed abnormal lung architecture despite the use of enzyme replacement therapy. Unfortunately, the underlying mechanism was unable to be elucidated in this report.

THYROID DISEASE

Thyroid disorders are not uncommon in patients with PH and may be often associated with sudden decompensation. The prevalence of thyroid disease in patients with PH is elevated, approximately 20% to 35%.[27-29] Correlations have been described between thyroid stimulant hormone and pulmonary artery pressure ($r = -0.82$; $P < .001$) and free thyroxine and pulmonary artery pressures ($r = 0.85$; $P < .001$).[28] The physiological effects of thyroid dysfunction have been associated with poorer outcomes in patients with PH.

Retrospective studies have suggested an association between thyroid disease and the diagnosis[30] or therapies[31,32] of PH, plus several case reports describe the associations between PH and thyroid disease. There are case series to suggest an association with PH and hyperthyroidism,[33-37] hypothyroidism,[27,29] or elevated antibodies. Zuhur and colleagues[36] described higher pulmonary vascular resistance in 35% of patients with Graves disease, 36% of patients with multinodular goiters, and 13.5% of patients with hypothyroidism.

Table 4. Mechanisms of Thyroid Disease in Pulmonary Hypertension

Hyperthyroidism	Hypothyroidism
Autoimmune phenomenon associated with endothelial damage or dysfunction	Autoimmune phenomenon associated with endothelial damage or dysfunction
Increase in catecholamine sensitivity, resulting in high cardiac output and endothelial damage	Vascular reactivity caused by a decrease in the levels of thyroid hormone
Increased metabolism of intrinsic pulmonary vasodilator (ie, prostacyclin and nitric oxide)	Decreased nitric oxide
Decrease metabolism of vasoconstrictors (serotonin, endothelin-1 and thromboxane)	Decreased arterial compliance and increased vascular resistance
Stimulation of sympathetic nervous system, causing pulmonary vasoconstriction	Inflammation (high C reactive protein and elevated interleukin 6)
Alteration of gene expression (inhibits calcium ATPase channels in the sarcoplasmic reticulum, increase adrenergic receptors)	Alteration of gene expression (decrease in adrenergic receptors)

A link between autoimmune processes and PH has been established, and interestingly thyroid disease can also be precipitated by autoimmune processes.[38] This has been shown in an observational study of 63 patients with PH who showed evidence of concomitant autoimmune thyroid disease in 49% of them,[39] and the authors found that in PH there was a higher prevalence of antithyroglobulin and antithyroperoxidase antibodies. There was no chronologic relationship between the diagnosis or treatment of PH and that of autoimmune thyroid disease. Importantly, 25% of the patient had first-degree family members with autoimmune thyroid disease. Yanai-Landau et al[40] also found 40 patients with PH in which 30% had antithyroglobulin antibodies. There is no clear explanation for this association. Additionally, bone morphogenetic protein receptor 2 mutations in adults and children with PH have been found patients with thyroid disease.[41]

Besides the autoimmune process, thyroid disease may also increase catecholamine sensitivity, enhance intrinsic pulmonary vasodilators, reduce pulmonary artery compliance, decrease vasoconstrictors, and generate high cardiac output states that can precipitate PH (Table 4). Some of these proposed mechanisms are supported by the reduction of pulmonary vascular resistance after euthyroid states are achieved.[42] Thyroid hormones affect growth and maturation of vascular cells and tissues, which affect the level of plasma membrane and endoplasmic reticulum influence over the calcium ATPase and transcellular membrane flux of cations and substrates, and consequently affect smooth muscle cells.[43] Specific thyroid regimens, like methimazole, induce immunoregulation by a direct inhibitory effect of thyrocytes, proportion of T help-like and T suppressor cells, that secrete vasoactive agents.[44]

Other than anecdotal reports, there is no clear evidence regarding the use of PH-targeted therapy for patients with PH and thyroid disease. The use of antithyroid medications, radioactive iodine, surgery, or combination of these therapies has demonstrated a reduction or normalization in pulmonary artery mean pressures.[28,34] An observational study revealed that 164 patients with mean pretherapy pulmonary arterial systolic pressure of 39 mm Hg could achieve mean posttreatment pressures of 30 mm Hg after antithyroid medications, radioactive iodine, and surgery.[27] The use of PH-targeted therapy has also been described in cases of thyroid dysfunction and PH. Menon et al[45] described 6 cases with hyperthyroidism and autoimmune goiter, in which 5 received intravenous prostacyclin (epoprostenol) and 1 received oral prostacyclin receptor agonist (selexipag). These authors concluded that targeting prostacyclin pathways was a potential risk factor for the development of symptomatic thyroid disease, since the patients developed Graves disease, Hashimoto disease, and thyrotoxicosis.

One of the less common side effects of prostacyclin-based PH medical therapy is hyperthyroidism, demonstrated with epoprostenol,[31] treprostinil, and selexipag.[46] In the event-driven, phase 3 trial, Prostacyclin (PGI2) Receptor Agonist In Pulmonary Arterial Hypertension (GRIPHON) study, the use of selexipag was associated with hyperthyroidism in 8 patients in the treatment arm (N = 574), compared to 0 of the individuals in the placebo group (N = 582).[46] Others have reported a prevalence of 6.7% of thyroid stimulating immunoglobulin negative thyrotoxicosis in adults with preexisting PH treated with epoprostenol.[47]

CONCLUSION

The data currently available indicate that glycogen storage disease and Gaucher disease are important metabolic disorders that have demonstrated an increased risk of PH and are included as a group 5 in the 6th World Symposium on PH classification. Thyroid disorders, while not included in the group 5 classification, are more prevalent, and have been associated with PH via various mechanisms. The real incidence of PH in these disorders is often unknown, although studies suggest PH can be common. The management is guided by small case reports, series. and observational studies, but overall treatment is directed toward treating the underlying disorder.

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