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Vildagliptin promotes improvement in pulmonary arterial hypertension: incretin-based therapy at a follow-up of 3 years

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Abstract

Arterial pulmonary hypertension (PAH) is a rare complication in patients with metabolic syndrome. A good glycemic control is related to a better prognosis in diabetic patients with PAH. The presence of GLP-1 receptors in the lungs and the fact that this incretin promotes vasorelaxation in the pulmonary artery, place the incretin-based therapy as a possible treatment in patients with PAH. This case report will show the effect of vildagliptin - a DPP4 inhibitor - on the improvement of pulmonary symptoms and hemodynamic patterns in a patient with type 2 diabetes mellitus and PAH.

Introduction

Pulmonary arterial hypertension (PAH) is a serious condition that causes pulmonary vascular resistance, right heart failure, and death [1]. In its current classification, the most common form of PAH is idiopathic [2]. A study shows that more than a third of patients with idiopathic PAH present criteria for metabolic syndrome (MS) [3].

MS is the association of two or more metabolic problems such as obesity, dyslipidemia, diabetes and hypertension [4]. Among the components of MS, obesity, dyslipidemia and diabetes stand out as important causes of pulmonary diseases, including PAH [5].

One of the pathophysiological changes related to type 2 diabetes (T2D) is the decrease in the incretin effect with a marked reduction in the serum levels of glucagon-like-peptide 1 (GLP-1) and, consequently, a decrease in insulin secretion. GLP1 is secreted by L cells into the distal intestine after carbohydrate intake and is cleaved rapidly by the enzyme dipeptidyl peptidase type 4 (DDP4) [6].

In vitro and studies with PAH-induced animals indicates that GLP-1 promotes vasorelaxation in the pulmonary artery [7,8]. Case reports show an improvement in the history of PAH in obese patients who underwent bariatric surgery, which in addition to reducing weight, also increases serum GLP-1 levels [9].

In order to prove the beneficial effect of GLP-1 in the treatment of PAH, one way to increase the levels of this hormone without inducing weight loss would be to use a class of oral antidiabetics, called DDP4 inhibitors. Next, we will report the case of a diabetic patient, obesity and with PAH after starting vildagliptin use.

Case report

A 74-year-old female patient was referred to an endocrinologist in February/14, reporting a previous diagnosis of T2D, dyslipidemia, hypertension and PAH. Physical examination had 67 kg, height 1.49m, body mass index (BMI) 30.2 kg/m^2 (obesity grade I), blood pressure 135 × 90 mmHg and dyspnea complaint. He used glyburide 5 mg/day, atorvastatin 20 mg/day and losartan 50 mg 2x/day. Laboratory tests indicated good metabolic control with glycemia of fasting 107 mg/dL, glycated hemoglobin (HbA1c) 6.2%, total cholesterol 122, HDL-c 58, triglycerides 100 and LDL-c 44. Even in the use of losartan, the patient had symptoms of pulmonary hypertension and transthoracic echocardiogram indicated systolic pressure of the right ventricule (SPRV) of 45 mmHg.

Despite the adequate value of HbA1c, the use of glyburide caused several episodes of hypoglycemia in the patient. With a view to better glycemic control, without the risk of hypoglycemia, and the possibility of increasing serum levels of native GLP1, we switched the sulfonylurea for a DDP4 inhibitor, vildagliptin 50 mg 2x/day to raise levels of native GLP-1.

After six months with the new oral antidiabetic, the patient returns with new exams and without any pulmonary symptoms reporting a significant improvement in dyspnea. At physical examination, he maintained the same weight and BMI, laboratory tests with glycemia of fasting 111 mg/dL and HbA1c 6.0%, without new episodes of hypoglycemia. A new echocardiogram indicated an improvement of the PAH picture with a SPRV of 38 mm Hg.

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During 3 years the patient remained asymptomatic and with good glycemic control. In the last consultation (January/17), still using vidagliptin 50 mg 2x/day, presented a weight of 68 kg, BMI 30.6 Kg/m^2 and the laboratory tests a fasting glycemia of 112 mg/dL and HbA1c 6.5%. The echocardiogram indicated a SPRV of 31 mmHg.

Discussion

Previous studies point to an important relationship between diabetes and PAH. The HbA1c dosage has a prognostic value at the time of the diagnosis of PAH. Patients with HbA1c> 5.7% had lower survival rates [10]. In patients with glucose intolerance and PAH, patients with HbA1c <6.0% obtained better respiratory evaluation on a 6-minute walk test [11].

The change in PPARgamma can lead to vascular damage in the pulmonary circulation and proliferation in the pulmonary circulation [3]. The use of rosiglitazone, a PPARgamma agonist, promoted pulmonary artery vasorelaxation in an *in vitro* study [12]. Another curious fact is the improvement of obese patients with PAH after undergoing bariatric surgery, which, in addition to inducing significant weight loss, also promotes an increase in incretin secretion, including GLP-1 [9].

Research shows the presence of GLP-1 receptors in the lungs [13]. In addition to several important metabolites, GLP-1 presents some pleiotropic effects that are still little known. Studies show that GLP1 in the lungs increases the production of surfactant [14], acts as an anti-inflammatory in acute respiratory failure [15], and also promotes vasorelaxation in the pulmonary artery [7,8].

Previously, we had already demonstrated this effect when using a DPP4 inhibitor (vidagliptin 50 mg 2x/day) in two obese patients with T2D and PAH. In both cases, after six months of the introduction of this type of oral antidiabetic without weight reduction, there was a significant reduction in SPRV [16].

In this three-year follow-up of one of these patients shows new effects of this drug. In addition to being a safe and effective medication for glycemic control of T2D, vildagliptin was also important in improving PAH, with reduction of SPRV in the first six months of treatment, and throughout this period, it was able to maintain normal levels of SPRV.

Conclusion

There is an important relationship between MS and PAH and different pathophysiological pathways of diabetes are interrelated with the onset of PAH. Despite the possible beneficial effect of weight loss, the increase in GLP-1 seems to have an important connection in the improvement of PAH. The use of DDP4 inhibitors or GLP-1 analogues are two interesting options for patients with T2D and PAH.

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