

Metabolic Connection between Incretins and Pulmonary Hypertension

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Abstract

Studies show that at least half the adult population is overweight in most countries. Recent case reports have shown the important metabolic potential of the pathophysiology of PAH. Many cases of PAH, etiologically classified as idiopathic, present an important interaction with insulin resistance, glucose intolerance and adiponectin deficiency. However, very little of these effects is operated GLP1 link receiver in his lung. About 20 years it is known of the presence of GLP1R lung and also the statement of GLP1 in vasorelaxation of pulmonary artery in animal models but few papers relating this incretin in the pathophysiology and treatment of PAH. The mimic incretins hypoglycemic drugs - the iDPP4 and GLP1a - would have a great therapeutic potential in diabetic patients with PAH. More studies are needed to evaluate the benefit of these medications in the treatment of PAH as well as its effectiveness of these effects in non-diabetic patients.

Keywords: T2DM; Pulmonary Arterial Hypertension; DPP4; NO

Background

Currently, diabetes and obesity are major metabolic diseases and a major worldwide epidemic. Studies show that at least half the adult population is overweight in most countries. With the increase in obesity is also increasing in prevalence of diseases that comprise metabolic syndrome such as hypertension, dyslipidemia, and type 2 diabetes mellitus (T2DM) [1]. Besides the classic diabetes-related complications such as retinopathy, nephropathy, neuropathy and the atherosclerotic diseases, such as myocardial infarction and stroke [2], other diseases emerge as potential complications of these metabolic changes, including pulmonary arterial hypertension (PAH) [3].

Many cases of PAH, etiologically classified as idiopathic, present an important interaction with insulin resistance [4,5], glucose intolerance [6] and adiponectin deficiency [7-10]. The formation of advanced glycation end products (AGE), increased by chronic hyperglycemia appears to be important in the development of PAH [11,12].

Low HDL-cholesterol levels are associated with worsening of PAH and the use of simvastatin has proved effective in preventing pulmonary fibrosis and improving physical function in patients with PAH [13,14]. Recently, it improved PAH was evidenced with decreased systolic right ventricular (SHV), as examination of transthoracic echocardiography in an obese patient with weight loss after undergoing bariatric surgery [4,15].

In the pancreas, the GLP1 receptor (GLP1R) are present on various cells in the human body and, for this reason, there are many pleiotropic effects as a result of the use of iDPP4 and GLP1 analogs (GLP1a) in the heart, kidney, liver, heart, fat, stomach, central nervous system, etc. [16,17].

However, very little of these effects is operated GLP1 link receiver in his lung. About 20 years it is known of the presence of GLP1R lung and also the statement of GLP1 in vasorelaxation of pulmonary artery in animal models but few papers relating this incretin in the pathophysiology and treatment of PAH [18,19]. Reduction of the incretin effect in the pathophysiology of T2DM, with decreased production of GLP1 and increase in enzyme activity DPP4 [20],

could explain the relationship between the HAP with the metabolic syndrome.

Thus, PAH has characteristic symptoms such as dyspnea, cyanosis, palpitations, persistent coughing, dizziness and syncope that could be related to other diseases and even other complications in an obese and diabetic patient. For this reason, it is important endocrinologists be attentive to the presence of some of these symptoms and suspicion of HAP request an echocardiogram to measure the RVSP or cardiac catheterization of the right chambers, gold standard for diagnosis of the disease [21].

Further, PAH occurs by an imbalance between vasodilator and vasoconstrictor agents, and the reduction of incretins could contribute to the vasoconstriction of the pulmonary artery and the development of PAH. Currently this condition is treated with medications and basic oxygen therapy for the treatment of PAH as anticoagulants, diuretics, calcium channel blockers, and more specifically phosphodiesterase-5 inhibitor (sildenafil), prostacyclin analogs, and endothelin receptor inhibitor (bosentan).

In addition to these medications, the mimic incretins hypoglycemic drugs - the iDPP4 and GLP1a - would have a great therapeutic potential in diabetic patients with PAH. More studies are needed to evaluate the benefit of these medications in the treatment of PAH as well as its effectiveness of these effects in non-diabetic patients.

The aim of this study was to evaluate the treatment in patients

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with and without diabetic that despite age, reported no episodes of hypoglycemia during the case study.

Methodology

In the first case, SPLM, patient 63-year-old female with a previous diagnosis of T2DM, obesity, hypertension and dyslipidemia forwarded to endocrine evaluation for better glycemic control and weight loss. He was wearing only metformin 100 mg day⁻¹ for glycemic control. In the second case, HFC, patient 74-year-old female with a previous diagnosis of T2DM about three years, obesity, hypertension, dyslipidemia osteopenia, vitamin D deficiency and pulmonary hypertension. Already had echocardiogram with 45 mmHg of SPRV and was followed up with a cardiologist. Because of the risk of hypoglycemia was chosen by the exchange of glyburide by vildagliptin 50 mg twice daily.

Analysis

In our recent work in 2015, two case reports have shown the important metabolic potential of the pathophysiology of PAH. In the present study, this is the first description in humans that use a iDDP4 (in this case, vildagliptin 50 mg twice daily) may be a treatment option for patients with PAH with T2DM by the presence of GLP1R in the lung. Thus, in the first case there was weight loss and improved glycemic level. In the second case, both the glucose level of the weight remained.

In both cases, using vildagliptin, there was a decrease in systolic pressure of right ventricle pointed out that the relaxation of pulmonary artery has a more beneficial effect would be mediated by NO and activation of vascular potassium channels, further of the effect direct by increasing GLP1, since the IRS1 less inhibited increases the activation of kinases, which in turn increases the stimulus for nitric oxide production in endothelial cells, reducing pulmonary arterial pressure.

Our group showed a reduction of SHV, also through echocardiography in two obese and diabetic patients after starting use of inhibitor of dipeptidyl peptidase (iDDP4) - in this case, vildagliptin 50 mg twice a day- in the treatment of T2DM. Unlike the case that weight loss after bariatric surgery, weight loss in the other two cases who received iDDP4 was insignificant in relation to the patient underwent surgery. As the use of a iDDP4 is capable of increasing the native GLP1, bariatric surgery also promotes the same metabolic disorder.

The interaction of SOCS3 with angiotensin II and with the proteins of the insulin signaling pathways prevents phosphorylation of IRS-1 and IRS-2 tyrosine and serine phosphorylation and activation of AKT (protein kinase). Thus, induction of SOCS3 by angiotensin II prevents the activation of JAK-2 via / STAT-5b by insulin. Therefore, SOCS3 is an interface in insulin signaling systems and angiotensin II.

Thus, insulin resistance, with inhibition of the insulin receptor (IRS1) leads to compensatory hyperinsulinemia and development of endothelial dysfunction, inhibited since the IRS1 prevents the activation of kinases that are involved in generation of the stimulus for the production oxide nitric endothelial cells. Thus, with decreased production of nitric oxide increases the pulmonary arterial pressure [22].

Conclusion

It was concluded that in the first case there was weight loss and improved glycemic level. In the second case, both the glucose level and the weight remained. In both cases, using vildagliptin, there was a decrease in systolic pressure of right ventricle.

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