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Pulmonary Artery Relaxation was Best with Increasing GLP1 than the Metabolic Improvement in Patients with Type 2 Diabetes

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Abstract

According to epidemiological data on type 2 diabetes (T2DM) represents about 95 % of cases of diabetes diagnosed, with projected to exceed 480 million in 2030. In addition, pulmonary arterial hypertension (PAH) has an estimated prevalence of 30 to 50 cases per million population, affects women more often than men, and PAH and T2DM are medical conditions that presents statistical correlation. The aim of this study was to evaluate the treatment in patients with diabetic that despite age, reported no episodes of hypoglycemia during the case study. Larger studies are needed to assess whether the same results are reproducible in diabetics and also euglycemic patients with PAH. Case 1, 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. Case 2, 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. In the present study, this is the first description in humans that use a iDDP4 may be a treatment option for patients with PAH by the presence of receptor GLP-1R in the lung. It was concluded that 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.

Keywords: T2DM; Pulmonary Arterial Hypertension; DPP4; NO

Introduction

According to epidemiological data on type 2 diabetes (T2DM) represents about 95 % of cases of diabetes diagnosed, with projected to exceed 480 million in 2030 [1]. About 2/3 of these individuals with T2DM live in developing countries, in younger age groups and that 60-90 % of patients with T2DM are obese, the highest incidence being after 40 years. Furthermore, it is known that type 2 diabetes has a hereditary factor greater than type 1. Still other disorders glucose considered previous stages to type 2 diabetes is also asymptomatic [2].

Added to this, the T2DM is associated with significant morbidity and mortality due to complications arising. The complications of diabetes are a huge cost to the national health services worldwide [3,4]. In the CODE-2 study estimated that the costs of treating the complications of T2DM are 3 times higher than disease control costs, before the onset of complications. So the hospital has more than 50 % of total costs, contrasting with the use of oral antidiabetics and insulin, which account for only 7% of the costs of health care [4,5].

Moreover, pulmonary arterial hypertension (PAH) has an estimated prevalence of 30 to 50 cases per million population, affects women more often than men. In addition, PAH and T2DM are medical conditions that present statistical correlation. Even in non-obese humans with idiopathic pulmonary arterial hypertension, the prevalence of insulin resistance is about 50% (1.2), suggesting a link between deregulation of blood glucose levels and pulmonary hypertension.

However, the interrelationship between pulmonary arterial hypertension and diabetes mellitus type II is comprised of the activation of intracellular kinase JAK2 (Janus kinase 2) by angiotensin 2, which directs the signal to the nucleus by the signal transducer protein (STAT) and activator of transcription. Moreover, suppressor of cytokine proteins (SOCS), especially SOCS3, can be induced by activation of the JAK/STAT pathway by several hormones, especially insulin and angiotensin II. Thus, it is suggested that SOCS3 proteins are potent inhibitors of insulin signaling, since SOCS3 expression is increased in various conditions associated with insulin resistance [6].

The main biochemical mechanism involved is the activation of the JAK/STAT/SOCS3 mediated by activation of the AT1 receptor, which in turn, determines the ubiquitination of insulin-responsive substrates [7]. Pharmacological control of hypertension should be instituted wherever possible with converting enzyme inhibitors of angiotensin (IECA), for the purpose of decreasing the activation of the AT1 receptor by angiotensin II, so thus minimize the effects of insulin resistance these patients [8,9].

Recent studies indicate an idiopathic PAH correlation with insulin resistance, glucose intolerance and adiponectin deficiency [1,2]. The prevalence of metabolic syndrome in idiopathic PAH is close to 50 %. Based on this, a group reported a case of a morbidly obese patient with idiopathic PAH who, after undergoing bariatric surgery had significant hemodynamic improvement after weight loss and metabolic improvement, even without changing the therapeutic regimen of PAH [2,3]. Unlike this report after bariatric surgery in which the focus was weight loss in improving PAH, our second case had no significant

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variation in weight, fasting blood glucose and glycated hemoglobin, and decreased the PAH after introducing a iDDP4 in the treatment of T2DM [3].

Thus, the benefits of tight control of blood pressure may be better than those obtained with the tight control of blood glucose levels. Still, according to Gomes et al. [10], the prevalence of hypertension among diabetics is 1.5 to 2 times higher than among non-diabetics. Extending studies, a group of scientists British performed for more than 15 years worldwide studies on the oral treatment of type 2 diabetes, with 5,200 patients testing all options and oral hypoglycemic antidiabetic agents results in the body. In conclusion, the results of the drugs were beneficial, greatly reducing the number of complications [11,12].

Thus, highlighting vildagliptin that controls blood glucose by reducing glucagon secretion and increased insulin secretion functioning as selective inhibitor of DPP4 enzyme that degrades GLP1 (glucagon like peptide-1), about 140 completed or ongoing research involving more than 12,400 patients thus inhibit the rapid degradation of incretin, vildagliptin increases levels of GLP1, this hormone being available to modulate the function of α and β cells [1,13]. Thus, vildagliptin shown to improve the function of β cells, as measured by insulin secretion rate dependent on the glucose [14,15]. The reaction mechanism consist in that vildagliptin has a nitrile group which readily forms a covalent bond with the catalytic site of DPP4 to form an imidate group that stabilizes the catalytic site vildagliptin DPP4 and facilitate the hydrolysis of the imidate group .

Furthermore, in response to these reports, the US FDA and the European Medicines Agency each undertook independent assessments of all clinical and pre-clinical trials relating to the possible association of DPP4 inhibitors with pancreatic cancer [2,16]. In a joint letter to the New England Journal of Medicines, the agencies said they "Both agencies agree that the statements about a causal association between incretin-based drugs and pancreatitis or pancreatic cancer are inconsistent with current data. Nevertheless, pancreatitis will continue to be considered a risk associated with these drugs [2,16].

The aim of this study was to evaluate the treatment in patients with and without diabetic that despite age, reported no episodes of hypoglycemia during the case study, showing that this is a very safe and effective medication. Larger studies are needed to assess whether the same results are reproducible in diabetics and also euglycemic patients with PAH.

Case Report

Case 1

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 1000 mg day^{-1} for glycemic control. On physical examination the patient had blood pressure of 150 × 100 mmHg, weight 137.8 kg and body mass index (BMI) of 62 kg m^{-2} (morbid obesity) Due to the marked dyspnea during the first consultation and auscultation with wheezing discrete, We were asked cardiopulmonary evaluation and tests for metabolic assessment of the case.

In initial tests the patient had fasting blood glucose of 178 mg dL^{-1}, blood glucose 2 hours postprandial 256 mg dL^{-1} and glycated hemoglobin -8.1%, spirometry with ventilatory mild obstructive disorder and echocardiogram presenting fraction Eject 63.1%, by Simpson's biplane method, a slight degree of LVH, LV diastolic dysfunction grade I (changing relaxation) and Sistolic Pressure of Right Ventricule (SPRV) degree with 51 mmHg. By uncontrolled blood glucose and the presence of PAH opted for the exchange of metformin by the association of vildagliptin 50 mg plus metformin 850 mg twice daily for decreased glycated hemoglobine and PAH without the association of any specific medication for treatment of PAH.

After six months the patient returns with reduced weight of 10 kg and with new laboratory tests that showed improved glycemic control with fasting glucose of 122 mg dL^{-1}, glucose postprandial 2 hours of 178 mg dL^{-1} and glycated hemoglobine 6.6%. Requested control echocardiogram showed the persistence of diastolic LV dysfunction grade I, but with an increase in ejection fraction to 73 % and decreased to 43 mmHg SPRV. Clinically, patients report partial improvement of dyspnea possibly related to obstructive lung disease.

Case 2

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. He reported dyspnea complaint only on moderate effort. On physical examination, the patient had a blood pressure of 130 × 80 mmHg, weight 67 kg and body mass index (BMI) of 30, 2 (obesity grade I) with no changes in lung auscultation.

At the first evaluation with an endocrinologist, patient reported to be using only glyburide 5 mg daily and keeping a good glycemic control with fasting glucose of 107 mg dL^{-1} and glycated hemoglobine -6.2% but at the cost of some episodes of symptomatic hypoglycemia. Because of the risk of hypoglycemia was chosen by the exchange of glyburide by vildagliptin 50 mg twice daily.

After 6 months, the patient returns for assessment with new tests. Refers improvement of dyspnea on exertion and good glycemic control without new episodes of hypoglycemia. She maintained the same body weight, fasting glucose 111 mg dL^{-1}, glycated- hemoglobin 6.0% and echocardiogram with SPRV of 38 mmHg.

Discussion

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. GLP1 is a substance derived from the cleavage of pro-glucagon, secreted from L cells in the distal intestine and rapidly cleaved by dipeptidyl peptidase 4 (DDP4) [17,18]. It has great importance in the pancreas and metabolism of glucose by increasing insulin secretion and decreasing glucagon. Recent publications have been emphasizing the pleiotropic aspects of GLP1 that go beyond glycemic control. There is evidence that its increase has extra-pancreatic effects by the presence of GLP1R in various tissues such as the heart, gastrointestinal tract, bones, central and peripheral nervous system, endothelial cells, kidney, macrophages, monocytes and lung [19-41].

According to Ciccone et al. [42], Diabetes mellitus worsening cardiovascular risk profile of affected individuals, being capable of inducing the expression of several morbidities that worsen the clinical condition of patients with decreased survival. Although detection of diabetes has increased the mortality rate of individuals because of their pathogenesis, and in the literature, there are many informations gaps on the role of pre-diabetes and diabetes mellitus, family history of the outcome of the general population.

Several studies have examined the relationship between idiopathic pulmonary hypertension with autoimmune thyroid disease. According to Ciccone et al. [43], it was demonstrated that patients with Hashimoto's thyroiditis did not show significant pulmonary hypertension compared to healthy controls.

Among these effects, a little studied is the presence of GLP1R in the lung. In 1988 these receptors have been identified in rat lung and subsequently showed that the use of GLP1 resulted in pulmonary artery vasorelaxation in these animals [3,40]. In 1995, Wei and Mojsov first described the presence of GLP-1R in various human tissues as well as lung, but no studies have shown the effects of GLP1 in the pulmonary vessels of humans [37]. Based on this information, our group have opted for the use of a DDP4 inhibitors (iDDP4) in the case VG at a dose of 50 mg twice daily, in two patients with PAH and T2DM associated and compared by echocardiographic data if there was a hemodynamic response with the use of a medication that increases native GLP1's half-life in circulation [27,28].

Previous studies have shown some effects of the presence of GLP1 as a therapeutic target promoting an increase in surfactant production by type II pneumocytes, protection of basal lamina of alveolar capillaries diabetic rats, anti-inflammatory action against acute respiratory insufficiency and in the treatment of patients with T2DM inhaled instead of daily subcutaneous injections [29,30]. However, no studies described in literature showing pulmonary artery vasodilation in humans mediated by GLP-1 increased with the use of iDDP4 or GLP-1 analogous [31,32]. The main symptom of PAH is dyspnea may be associated with palpitations frame, cyanosis, persistent cough, dizziness or syncope [33].

The same is defined as an increase in mean pulmonary artery pressure at rest ≥ 25 mmHg on catheterization of the right chambers of the heart causing an increase in pulmonary vascular resistance due to the following factors: vasoconstriction, obstructive remodeling of the pulmonary vessels, inflammation and thrombosis in situ. In pulmonary vascular dysfunction occurs decrease of vasodilator substances such as nitrous oxide (NO) and prostacyclin, and increase of vasoconstrictors such as endothelin-1 and thromboxane [34,35].

Furthermore, 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 [41]. 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.

Recent studies ACCORD, ADVANCE and VADT have generated some controversy on glycemic control intensive, suggesting that there will need to set sound strategies and adequate for certain profiles of patients [1,34]. In the ACCORD and VADT studies was established an association between severe hypoglycemia and CV risk, although it is not yet possible to establish a clear cause-effect relationship. In this context, a DPP4 inhibitor was added to the patients in this study, replacing some drugs in 41 % of patients (sulfonylurea and glitazone) to optimize glycemic control without increasing the risk of hypoglycemia, cardiac insufficiency, causing no increase weight or edema [1,2,36].

In the present study, vildagliptin was always added to patients taking metformin in case 1. The rationale for this combination of metformin with a DPP4 inhibitor is a complementary mechanism of action. Metformin improves insulin sensitivity in muscle and liver, and in turn, vildagliptin increases GLP1 levels of improving dysfunction α and β cells. The use of fixed combination vildagliptin and metformin may be an additional advantage, since it has been shown that a fixed combination improves adherence [3,4].

Furthermore, as other strengths vildagliptin of use, there was a suppression of the levels of postprandial glucagon during the night, benefiting the reduction in fasting glucose, besides the reduction of glycated hemoglobine- at 0.7%, 1.3% and 1.8% in patients with early glycated hemoglobin 7.5%, 8.5% and 10%, respectively [14]. Moreover, the glucagon-sensitive response to glucose improves not only blood glucose, but also appears to reduce the risk of hypoglycaemia when vildagliptin is used in combination with other drugs associated [15].

In addition, the vildagliptin has also been extensively studied as monotherapy and in combination with other oral antidiabetic agents such as metformin, sulfonylurea, and glitazone insulin, with good results [16]. Added to this, after analysis of vildagliptin database, involving more than 8,000 patients participating in clinical trials confirmed the safety and efficacy of the drug. It has been shown also lower frequency elevation of liver enzymes in patients taking vildagliptin 50 mg once or twice daily, as compared to those who received 100 mg once daily [17].

On suspicion of PAH, echocardiography can help diagnose the presence of tricuspid regurgitant jet velocity >3.4 m s^{-1}, a systolic pulmonary artery pressure > 50 mmHg with or without other changes suggestive of PAH with a strong level of evidence, however, must be confirmed by cardiac catheterization [3,35,37]. However, echocardiography can also assist in PAH with patient follow-up in the assessment of prognosis. The treatment of PAH is to some general measures such as oxygen therapy, and drug therapy with anticoagulants, diuretics, calcium channel blockers, digoxin, and more specifically, the use of phosphodiesterase-5 inhibitors (sidenafil), prostacyclin analogues inhibitors and endothelin receptor antagonists (bosentan) [4].

There is a gap in information results would be what the actual mechanism of vasodilation induced by iDDP 4 as shown with vildagliptin in patients with T2DM [2,3,38]. Recent studies show that this effect would be mediated by NO and activation of vascular potassium channels, independent of the effect direct GLP-1 to your receiver. Improvement in echocardiographic patterns could also be a cardioprotective effect of GLP-1 [1-3]. The limitations of the study pointed out the short period between assessments, the fact that the echocardiogram is an operator-dependent examination and not performing the catheterization of the right heart chambers to better diagnostic evaluation and follow-up for the two cases. Another limitation is the serum basal not GLP-1 and after study termination with decreasing PAH.

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 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.

Final Considerations

In the present study, one of the main limitations was that only PAH was assessed by echocardiography. Moreover, its need to increase worldwide the number of blind studies with and without diabetes in an attempt to increase the accuracy of results and give more emphasis on benefit activation of GLP1 receptor for improved PAH.

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Disclosure of Potential Conflicts of Interest

The authors declare that they have no conflicts of interests.

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