

Triple Therapy with Empagliflozin, Linagliptin and Gliclazide in a Patient who Refuses Insulin: New Solutions to an Old Problem

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Case Report

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Abstract

Background: Insulin therapy refusal is a common subject in the routine of endocrinologists. New therapeutic options can work around this issue.

Objective: To report a case of insulin therapy refusal in a type 2 diabetes patient and how this was handled.

Design: Interventional case report with clinical and laboratory correlation.

Case Report: 54-year-old man receiving Metformin, 1.7g/d for 2 weeks. Triple oral therapy was considered after refusing insulin. Clinical evaluation and assessment of metabolic profile were completed on admission and 3 months later. The outpatient record was also reviewed.

Discussion: The triple therapy with Gliclazide, Empagliflozin and Linagliptin promoted laudable glycemic control, besides additional benefits in the blood pressure and weight loss.

Conclusion: Facing the patient's refusal or disinterest to use insulin, new classes of oral antidiabetic drugs are required.

Keywords: DPP-4 inhibitors; SGLT2 inhibitors; Combination therapy; Type 2 diabetes

Introduction

Over the past decades and since the release the first oral antidiabetic agent, several studies have focused on better therapeutic strategies for the treatment of diabetes. A large number of discussions have already been raised regarding insulin refusal amongst patients with type 2 diabetes [1]. Since the choices available for oral antidiabetic medications were quite limited till recently, discussion such as this were much more common in

medical offices [2]. Nowadays, with the development of new drugs and strategies for diabetes type 2 management we could soon start seeing more patients asking for insulin-free treatment.

Objective

To report a case of an obese patient with type 2 diabetes who had poor glycemic control and refused to consider changing his oral treatment to insulin.

Design

Interventional case report with clinical and laboratory correlation.

Presentation of Case

A 54 years-old white male (116.5 kg, BMI 39.38 kg/m²) with just 2 weeks history of type 2 diabetes mellitus (DM) started to take Metformin 850 mg twice a day without medical supervision. He also reported symptoms such as dry mouth, associated with tingling and cramps in the legs at night. This subject is a bakery owner, with a sedentary lifestyle and irregular eating habits; additionally he denies drinking alcohol or smoking. He was also diagnosed with hepatic steatosis and balanoposthitis six months ago and was treated accordingly. Capillary blood glucose levels ranged from 300 to 360 mg/dl, however it got reduced to around 270 mg / dl after introduction of oral antidiabetic medication. He is also under current treatment

for hypertension using Losartan/Hydrochlorothiazide 100 mg/25 mg daily. Clinical laboratory tests: fasting plasma glucose (FPG) 281 mg/dl, glycated hemoglobin (Hb A1c) 14.8%, serum creatinine 1.7 mg/dl, uric acid 10.4 mg/dl, normal thyroid and liver function; Total cholesterol (CT), HDL, LDL and triglycerides levels were 274 mg/dL, 40 mg/dl and 143 mg/dl, 243 mg/d, respectively. The patient vehemently refused being treated with insulin. Based on the above results, we prescribed Gliclazide 60 mg/d, Empagliflozin 25 mg/d, Linagliptin 5 mg/d, Rosuvastatin 10 mg/d and Allopurinol 300 mg/d. In addition, we referred the patient to a nutritionist and a cardiologist for further evaluation. Three months later, the end result was a weight loss of 35.5 kg (BMI 27.38 kg/m²), with complete normalization of all metabolic parameters: (FPG) 107 mg/dl, glycated hemoglobin (Hb A1c) 6.2%, serum creatinine 1.3 mg/dl, uric acid 4.6 mg/dl, Total cholesterol (CT), HDL, LDL and triglycerides levels were 119 mg/dL, 36 mg/dl and 68 mg/dl and 75 mg/d, respectively (see Table 1).

	On Admission	Three Months Later
Glycated Hemoglobin (HbA1c)	14.80%	6.20%
Fasting glucose	281 mg/dl	107 mg/dl
Post-prandial glycemia	297 mg/dl	148 mg/dl
Total cholesterol (CT)	274 mg/dl	119 mg/dl
LDL-c / HDL-c	40 / 143 mg/dl	36 / 68 mg/dl
Triglycerides	243 mg/dl	75 mg/dl
eGFR (MDRD)	79 ml/min/m ²	Not performed
Urine sample	Negative	Negative
Blood pressure (BP)	145/80 mmHg	130/70 mmHg
Weight/BMI	116.5 Kg / 39.38 kg/m ²	81 Kg / 27.38 kg/m ²
Abdominal circumference (AC)	132 cm	105 cm

Table 1: Type 2 diabetes clinical and laboratory parameters for the patient being studied.

Discussion

Despite several proven benefits, metformin usage was contraindicated for the patient due to the high possibility of renal failure, as indicated by high levels of serum creatinine.

An estimated GFR (eGFR) calculated from serum creatinine levels to assess kidney function, we identified that the association of sulphonylureas, empagliflozin and linagliptin could promote improvement for the glycemic profile while controlling and reducing weight and blood pressure [3-5]. The excellent glycemic control achieved within a short period of time suggests an improvement

in the glucotoxicity and lipotoxicity through these oral medications [6], nevertheless these results could as well be linked to the substantial weight loss achieved by the patient as he adjusted to a healthier lifestyle, based on good nutrition and physical activity.

Conclusion

Since diabetes is chronic disorder that requires successive interactions between doctor and patient in order to achieve the best form of treatment for glucose control, many times these doctor's visits could end up

stressing the doctor-patient relationship should certain treatment option be forced upon the patient. Nowadays many type 2 diabetes patients are refusing insulin therapy in favor of newer oral medications that could provide similar not to say the same clinical results as they would have achieved with insulin. Over the past ten years the boundaries on what can be done as far as diabetes therapy goes have been pushed above and beyond with the emergence of newer classes of oral antidiabetic drugs (see Table 2) [7,8]. It was not until recently when the Scientific community started to explore newer mechanisms for glucose control based on the digestive and renal systems. As awareness has been shown upon

these new options, strong beneficial effects have been recognized, such as the β -cell function preservation promoted by inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors or gliptins) [7,9,10], along with reduction of the blood pressure, loss of fat mass and decreasing microalbuminuria, particularly with the outstanding results by SGLT2 inhibitors [7,11].

Facing the patient's refusal to use insulin, a good innovative approach that includes oral medication with different mechanisms of action is bringing an exciting new pathway that now opens up for discussion [12,13].

Antidiabetic Drugs	Mechanisms of Action	Final Effect
SGLT2 inhibitors (Empagliflozin)	Inhibit renal glucose reabsorption	Reduction of Hyperglycemia
α -Glucosidase Inhibitors (Acarbose)	Inhibit absorption of carbohydrates	
Biguanides (Metformin)	Inhibit absorption of carbohydrates Reduce peripheral insulin resistance Reduction of hepatic glucose production	
Sulfonylureas (Gliclazide)	Stimulate the release of insulin	
Glinides (Repaglinide/Nateglinide)	Stimulate the release of insulin	
Thiazolidinediones (Pioglitazone)	Reduce peripheral insulin resistance Reduction of hepatic glucose production	
DPP-IV Inhibitors (Linagliptin)	Suppress the degradation of a variety of bioactive peptides, including glucagon-like peptide-1 (GLP-1)	

Table 2: Classes of oral antidiabetic drugs, its mechanisms of action and the expected final effect.

Conflicts of Interest

The authors report no conflicts of interest in this work.

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