



CASE REPORT

Empagliflozin managed Type 2 Diabetes Mellitus in Insulin induced Hypertension: A Case Report

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Abstract

Insulin is an essential hormone and has been the cornerstone in the therapy of Diabetes Mellitus. This case highlights insulin-induced hypertension in a type 2 DM patient, managed adequately with empagliflozin. A 60-year female with Diabetic Nephropathy & Hypothyroidism presented with elevated blood pressure after a week of insulin administration. An elevation in the patient's blood pressure corresponding to the administration of insulin was observed. De-challenge and re-challenge of insulin with dose adjustment, resulted in sudden spike & decrease of blood pressure, thereby pointing a suspicion towards a relation between insulin and hypertension. Discontinuation of insulin and replacement with oral hypoglycemics has resulted in controlled blood pressure levels.

Introduction

Insulin Resistance can lead to hypertension conversely, hypertension too can lead to insulin resistance. This report highlights insulin resistance preceding hypertension in a case with many co-morbid ailments. There are various pathways of insulin resistance elevating blood pressure. The immediate response of insulin resistance is hyperinsulinemia as a compensatory mechanism. Further steps in insulin-induced hypertension comprise of, structural changes in the artery, activation of the sympathetic nervous system, increased renal sodium reabsorption, changing transmembrane electrolyte transport [1]. Re-challenge and De-challenge of insulin have precluded all the other causes of hypertension, in this case, culminating it to be the cause for the increase in blood pressure.

Reason for report: To our knowledge, this is the first case report of insulin-induced hypertension with its management with Empagliflozin. This report can augment treatment, prognosis, morbidity, and

mortality of patients undergoing insulin therapy and its associated complications.

Case Report/Case Presentation

A 60 year old obese female patient with Type 2 diabetes mellitus with diabetic nephropathy and hypothyroidism since two years was admitted to a secondary care hospital. Her past medication history included metformin 500mg bd and levothyroxine 50mcg OD. The patient's vitals were normal and she was normotensive, with laboratory investigations significant for her elevated blood sugar and lipid levels. 20 IU of regular insulin at bedtime and 5IU of insulin aspart twice daily were newly added to her therapy since the patients' glycaemic control was poor.

The patient's characteristics and laboratory investigations are summarised in Table 1. Important parameters noted in this case were elevated blood pressure, sodium levels and heart rate. The addition of insulin was the only change made in the prescription

which gave rise to a suspicion of insulin induced hypertension. Insulin was de-challenged i.e withheld for the next 24 hours and the patient was treated with Metformin 500 mg bd and glimepiride 2 mg bd .To further confirm the exact cause for hypertension, 10 U of regular insulin was reintroduced (re-challenged) under the supervision of the treating physician by monitoring her blood pressure, heart rate and sodium concentration before and after the dose, as depicted shown in Table 2. There was a clear clinical evidence of insulin induced hypertension denoted by the alteration of parameters with de-challenge and re-challenge of insulin.

Outcome: Since the patient's blood glucose levels were consistently elevated, considering the risk/benefit ratio, T. empagliflozin 25mg od was initiated. Response to this modified therapy is shown in Table 3.The patient's blood pressure saw a downward trend over the next 3 days. Once the blood sugar levels were under control and her general condition was stable the patient was discharged with T. empagliflozin 10mg od along, atorvastatin-40mg and counselled to follow a diabetic diet with exercise as feasible, along with her past medication- levothyroxine. The Patient was advised to follow-up after 15 days.

Discussion & Conclusion

Insulin-induced hypertension and hypertension-induced insulin resistance has limited concrete clinical evidence. It must be noted that not all patients treated with insulin are likely to develop hypertension, certain factors that pose a greater risk to an individual for its likely development and which was prominent in our patient are:

- **High BMI:** Obesity in our patient could have precipitated elevation in BP due to insulin-resistance [2].
- **Large Waist Circumference** of 39.6 cm could have also contributed by activation of the sympathetic system and promotion of anti-natriuretic activity.
- **High Sodium Levels:** A study by SU Persson states that patients on insulin therapy had developed high blood pressure along with elevated serum sodium concentration owing to the alteration of transmembrane ion transport and increased renal sodium reabsorption [3].

This is in concurrence with our observation, as de-challenge of insulin led to the return of sodium levels to normalcy [4].

- **Decreased Insulin Clearance:** Klaus Rave et al stated a 40% decrease in insulin clearance in patients with diabetic nephropathy causing Hyperinsulinemia [5, 6].The other risk factors posed by our patient was being female. Lastly, due to diabetic nephropathy, the patient's laboratory parameters were significant for microalbuminuria associated with insulin resistance by abnormal generation of nitric oxide leading to defect in endothelium relaxation [7].

An important aspect to focus in this case is that the patient's blood pressure was normal during admission and an elevation in blood pressure level was noted with the administration of regular insulin, conversely reduction when insulin was withheld was also observed. Notably, we observed a rare rapid onset of hypertension after one week of administration of insulin, while existing evidence highlights an association of hypertension after months of insulin administration [8].Presently, there is no standardized therapy for the treatment of insulin induced hypertension.

We had incorporated empagliflozin in our treatment plan, as it is superior to other drugs in the SGLT-2 co-transporter inhibitors class with a better efficacy and safety profile [9]. The selection of this SGLT2 inhibitor over the others has not only resulted in regulation of the patient's blood sugar levels but also controlled increasing blood pressure, as many studies report the lowering of blood pressure with the treatment of empagliflozin. This finding is in concurrence with a systematic review and meta-analysis conducted by Zhao D [10].

Weight loss and cardio-protective effects are some added benefits of Empagliflozin that further guided our selection. Thus from our experience we recommend treating insulin induced hypertension with SGLT-2 inhibitors, as many of their pharmacological actions are directed towards risk factors of insulin resistance. The management of insulin resistance in Type 2 Diabetes can be dependent on the discretion of treating physicians with suitable consideration of the individual patient's parameters with appropriate tailoring of therapy.

Table 1: Patient characteristics and laboratory findings on admission

Physical findings	
Age	60 yrs.
Weight	97 kg
BMI	30.27
Waist Circumference	39.6 cms
Pulse rate	80 beats/min
Laboratory findings	
Fasting Blood Glucose (FBG)	190 mg/dL
Random Blood Glucose (RBG)	300 mg/dL
Post Prandial Blood Glucose (PPBG)	260 mg/dL
Glycated Haemoglobin (HbA1c)	8%
Total Count (TC)	220mg/dl
Low Density Lipoprotein (LDL-C)	176 mg/dL
High Density lipoprotein (HDL-C)	28 mg/dL
Total Cholesterol (TC)	289mg/dL
Glomerular Filtration Rate (GFR)	61 ml/min/1.73 m ² (eGFR using CKD-Epi)
Serum Creatinine (Sr. Cr)	1.0 mg/dL
24/Urine protein	56 mg protein
Spot urine creatinine ratio	Normal
Renal Ultrasound	Normal study
Blood Pressure	120/80 mmHg
Sodium	138 mEq/L
Potassium	3.5mE/L

Table 2: The effect of insulin on blood pressure, sodium levels and Heart rate

Parameter	Prior to insulin administration	Dechallenge of insulin				Within 12 hours of Rechallenge of 10 IU insulin
		1 st hour	8 th hour	12 th hour	24 th hour	
Sodium Levels	138mEq/L	152mEq/L	152mEq/L	151mEq/L	140mEq/L	146mE/L
Blood Pressure	120/80mm Hg	170/90 mm Hg	166/86mm Hg	163/86mmHg	156/80mmHg	165/85 mmHg
Heart Rate	75bpm	88bpm	90bpm	86bpm	81bpm	86bpm

Table 3: The effect of on blood pressure, sodium, heart rate and FBG after discontinuation of insulin and starting with Empagliflozin

Parameter	Treatment with Empagliflozin		
	Day 1 of treatment initiation	Two weeks after treatment initiation	Four weeks after treatment initiation
Sodium	146mEq/L	140mE/L	138mE/L
Blood Pressure	165/85mm Hg	135/80mmHg	120/80mmHg
Heart Rate	86bpm	78bpm	76bpm
Fasting Blood Glucose	180mg/dl	156mg/dl	132mg/dl

In patients with Type 2 Diabetes with significant insulin resistance, to avoid insulin induced hypertension, especially in those who are significantly overweight, lifestyle modifications must be recommended as the primary step in treatment, as in the case of our patient. The next step, or in some patients the first step, would be the initiation of a suitable oral hypoglycaemic agent.

Conclusion

Most health care professionals are unaware of the effect of insulin elevating blood pressure in specific patients mainly Type 2 diabetes with insulin resistance and other

comorbidities, as it is often masked or overlooked. Hence, if patients pose risk factors predisposing them to the same, it is essential to monitor blood pressure regularly in patients on insulin therapy, newly initiated or even otherwise, in order to optimize selected therapy, minimize morbidities and maximize the affected individual's quality of life.

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