Use of a sodium–glucose cotransporter 2 inhibitor, empagliflozin, in a patient with Rabson-Mendehall Syndrome

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Abstract

Rabson-Mendenhall Syndrome (RMS) is a rare condition caused by mutations in the insulin receptor gene. The affected patients have severe insulin resistance and the treatment is challenging due to difficulties in reaching satisfactory glycemic control. We report a case where iSGT2 was used as an adjunct therapy to insulin.

Full Title: Use of a sodium–glucose cotransporter 2 inhibitor, empagliflozin, in a patient with Rabson-Mendehall Syndrome

Short Title: Empagliflozin in Rabson-Mendehall Syndrome

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Ethics: Written informed consent was obtained from the patient's parents

S.S.S is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Keywords:

"Diabetes Mellitus/genetics"

"Acanthosis Nigricans/genetics"

"Insulin Resistance/genetics"

"Sodium-Glucose Transporter 2 Inhibitors"

"empagliflozin"

Introduction

Rabson-Mendenhall Syndrome (RMS) is a rare condition of autosomal recessive inheritance caused by mutations in the insulin receptor (INSR) gene. The affected patients have severe insulin resistance (SIR) and, the treatment is challenging due to difficulties in reaching satisfactory glycemic control (1).

Method

We report the therapeutic response to a sodium-glucose cotransporter 2 (SGLT2) inhibitor associated with insulin in a patient with Rabson-Mendenhall Syndrome. Written informed consent was obtained from the patient's parents.

Case Report

The proband is an 11-year-old boy, the first child of a healthy African-Brazilian distantly related parents. He was born at term with a birth weight of 2230 g, length of 45 cm (both below the third percentile). At the age of 6 months, he was diagnosed with diabetic ketoacidosis (blood glucose: 600 mg/dl, ketonuria: ++ and Bicarbonate 8 meq-L) when treatment with insulin was initiated. At the age of 1-year and 8-months, the patient was referred to our University Diabetes Center. Physical examination revealed a paucity of adipose tissue, severe acanthosis nigricans in axillae and neck, macrogenitossomy, hypertrichosis, acrochordons and premature dentition. He also had coarse facial features with flat nasal root, large and prominent ears and prognathism. His developmental milestones were delayed and growth retardation was observed. Biochemical analysis showed fasting plasma glucose: 79 mg/dl, HbA1C: 6.9%, Fasting C-peptide: 5.3ng/ml, anti-glutamic-acid decarboxylase antibody negative and normal lipid profile. Based on medical history and clinical findings, Rabson-Mendenhall Syndrome was hypothesized. Sequencing the *INSR*identified two variants: a missense mutation in exon 19 (NM_000208.3: 3845C>T, p.Ala1162Val) and an intronic variant located in the canonical splice acceptor site of intron 3 (c.975-2A>T). The former variant was already described in a Brazilian patient with RMS (2) and the latter variant was not previously reported and, the in silico bioinformatic tool Mutation Taster predicted that the variant is disease causing. Given the patient's clinical characteristics, compound heterozygosity was considered. He was maintained on insulin therapy until the age of 2.5 y (Determir 3 U/day), when due to several episodes of hypoglycemia, this medication was stopped (HbA1c: 6.2%, fasting C-peptide: 13.2 ng/ml). However, one year later persistent hyperglycemia returned, and insulin was reintroduced. Insulin doses has been titrated up over the years to 5.7 UI/kg/day. Metformin and pioglitazone were included in the therapy. Despite this, a progressive worsening of hyperglycemia occurred, with levels of glycated hemoglobin reaching 10.5% and fasting C-peptide decreasing to 1.7 ng/ml. Given that the SGLT2 inhibitors promote a reduction in blood glucose by enhancing urinary glucose excretion in a mechanism independent of insulin action and that some previous reports show the efficacy of this class of drugs in genetically induced severe insulin resistance, treatment with empafliflozin was considered. Recombinant IGF-1 and metreleptin, a recombinant human methionyl leptin, also have been used in patients with severe insulin resistance but due to their unavailability in our country and high cost, we could not consider them as an option. The parents were informed about the off-label use of empaglifozin and possible adverse events and agreed with its prescription. Empaglifozin was started at a low dose (2.5

mg/day) in addition to insulin and metformin, rising two months later to the current dose of 5 mg/day, with a strict monitoring of adverse effects mainly ketonemia. After 7 months of empaglifozin, HbA1c decreased to 7.7% (reduction of 2.8% from basal) and insulin dose could be reduced in 30% (table 1). The patient underwent series of blood β-hydroxybutyrate test, which results were in the range of 0.1-0.5 mmol/l.

Discussion

We report the case of severe insulin resistance due to a compound heterozygosity for two mutations in the *INSR* . Management of the hyperglycemia in patients with RMS is challenging, and the case here presented illustrates this difficulty: despite of high insulin dose associated with two classes of insulin sensitizers, desirable glycemic control was not achieved. Introduction of an SGLT2 inhibitor promoted a decrease of HbA1c from 10.5% to 7.7%, higher than the decrease observed when metreleptin or recombinant human IGF1were used in patients with SIR (3). Increase in blood ketone bodies was not detected during the treatment. Previous reports of treatment with SGLT2 inhibitors in patients with severe insulin-resistance syndromes were in cases of generalized lipodystrophy, SHORT syndrome and type A insulin resistance syndrome (4,5).

Conclusion

SGLT2 inhibitors, acting through an insulin-independent manner, is effective and safe in individuals with type 2 diabetes, and the case here presented demonstrated its effectiveness in a patient with RMS. Therefore, addressing other ways of reducing blood glucose that does not depend on the action of insulin per se as SGLT2 inhibitors could be an adjunctive therapeutic option in Rabson-Mendenhall Syndrome.

Author Contributions:

S.A.D, M.L.G, R.S.M and L.A.L.R contributed to the discussion and reviewed and edited the manuscript. S.A.D., M.L.G , R.S.M and S.S.S. performed the literature search and researched data and wrote the manuscript.

S.S.S is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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Table 1

Table 1: HbA1c and insulin dose during seven months therapy with empagliflozin.

	Before empagliflozin	**3 months of follow-up**	**7 months of follow-up**
Empagliflozin (mg/day)	0	2.5	5

	Before empagliflozin	**3 months of follow-up**	**7 months of follow-up**
HbA1c (%)/(mmol/mol)	10.5% / 91	8.1% / 65	7.7% / 61
Insulin dose (U/kg/day)	5.7	5.4	4.2