

## Forum

Sodium Glucose  
Co-transporter  
Inhibitors in Patients  
with Acromegaly and  
DiabetesZaina Adnan <sup>1,\*</sup>

**Acromegaly per se predisposes to diabetes. Somatostatin analogs (SSAs) have an overall neutral effect on glycemic control. However, a marked increase in hyperglycemia was observed recently since the introduction of pasireotide long-acting release (PAS-LAR). Sodium glucose cotransporter inhibitors (SGLT2is) have proven their efficacy, cardiovascular safety, and superiority in the management of type 2 diabetes mellitus (T2DM). However, this class is rarely recommended for patients with diabetes and acromegaly. A decreased circulating insulin level is considered unique for this class and might have a beneficial role in the growth hormone–insulin-like growth factor-I (GH–IGF-I) axis. Therefore, SGLT2is should be considered in the management of diabetes in patients with acromegaly.**

**Introduction**

Acromegaly is a rare chronic disease mainly caused by GH pituitary adenoma with increased levels of GH and IGF-I. Diabetes mellitus increases cardiovascular morbidity and mortality in patients with acromegaly [1].

GH and IGF-I play an important role in intermediary metabolism and excess GH causes insulin resistance,  $\beta$  cell dysfunction, and predisposition of patients with acromegaly to develop diabetes mellitus. Moreover, therapy with PAS-LAR causes worsening of pre-existing diabetes and the development of new-onset diabetes, while first-generation SSAs have an overall neutral effect on glycemic control [2–4]. It is noteworthy that GH excess promotes fluid retention and weight gain, and this negative effect should be taken into consideration during diabetes management in acromegaly.

SGLT2is are used in patients with T2DM. Despite their cardiovascular safety and superiority, which are similar to incretin-based therapy, in particular, glucagon-like peptide 1 receptor (GLP-1Rc) agonists, SGLT2is are not recommended for patients with acromegaly and diabetes. There are at least three important positive aspects of this class that should be taken into consideration: (i) cardiovascular superiority beyond glucose control; (ii) weight reduction and osmotic diuresis; and (iii) decreased insulin levels that might play an important role in GH receptor (GHR) expression, which results in decreased IGF-I levels [5,6]. The aim of this article is to focus on the role of SGLT2is in this group of patients and the potential additive effect of this novel class in patients with diabetes and acromegaly already under treatment.

**SGLTis as a Unique Class**

The antidiabetic effect of SGLT2is is achieved through a unique mode of action by promoting glycosuria. Furthermore, a significant fall in fasting plasma insulin concentration is demonstrated without significant increase in glucagon response. It is important to note that despite the reduced insulin secretion,  $\beta$  cell function and insulin tissue sensitivity to glucose uptake are improved [6].

**Insulin Levels and Hepatic GH Sensitivity**

Insulin modulates the biological activity of GH and IGF-I. It is well known that prolonged fasting induces gradual decline in IGF-I levels. A study by Leung *et al.* using the human hepatoma cell line HuH7 demonstrated a marked increase in hepatic GHR biosynthesis and surface translocation in response to insulin [7]. Moreover, decreased insulin levels and IGF-I concomitantly with increased IGF binding protein 1 were demonstrated in patients with GH deficiency treated for 7 days with octreotide and GH [8]. The recently published data by Droste *et al.* analyzing the results of the German cohort of the ACROSTUDY showed that patients with acromegaly and diabetes achieved lower response with pegvisomant (PEGV), and normalization of IGF-I levels was achieved to a smaller extent than patients without diabetes (64 vs 75%,  $P = 0.04$ ). Moreover, patients with diabetes required a higher dose of PEGV for IGF-I normalization (18.87 vs 15.50 mg/day,  $P < 0.01$ ), especially in those treated with insulin (22.83 vs 17.22,  $P = 0.11$ ). However, no significant difference was observed between diabetic patients treated with insulin versus oral agents [9]. Suppression of insulin secretion induced by SSAs is considered a negative effect on glucose metabolism despite its positive effect of inducing reduced expression of GHR on the hepatocyte surface, resulting in hepatic resistance to GH and decreased IGF-I production. These findings confirm previously published observations in which higher normalization rates of IGF-I levels were achieved in nondiabetic patients [10].

Treatment of diabetes should take into account the above-mentioned data. Choosing antidiabetic therapy for patients with acromegaly should take into consideration that circulating insulin levels play a pivotal role in modulating the activity of IGF-I, and that hyperinsulinemia has a

negative effect upon normalizing IGF-I levels.

### Euglycemic Diabetic Ketoacidosis (EuDKA) in Patients with Acromegaly and Diabetes

It is well known that SGLT2is may induce EuDKA, mainly in patients with insulin deficiency such as type 1 diabetes (T1DM), latent autoimmune diabetes of adults (LADA), and T2DM treated with insulin. The mechanism behind this complication is not fully elucidated. A suggested potential mechanism for SGLT2i induction of EuDKA is increased glycosuria in the presence of an increased rate of gluconeogenesis and free fatty acid release concomitantly with reduced insulin dose in patients treated previously with insulin [11]. Furthermore, the increase in plasma glucagon levels increases the propensity toward ketone production. It is noteworthy that GH itself increases lipolysis, lipid oxidation rate, and ketone bodies. These effects may potentiate the appearance of EuDKA in patients with unrecognized acromegaly treated with SGLT2is. The appearance of EuDKA in patients with already diagnosed and treated acromegaly using SGLT2is seems to be rare, particularly in patients treated with PEGV as monotherapy, or in combination with long-acting somatostatin analogs (LA-SSAs), where the potential mechanisms for this complication are attenuated (see below). Therefore, SGLT2i therapy might be considered in diabetic patients with acromegaly already under treatment in order to prevent this rare complication.

### Why SGLT2is in Patients with Diabetes and Acromegaly Might Have an Additive Effect?

The use of SGLT2is for patients with diabetes and acromegaly seems to be favorable. The significant fall in insulin levels might promote an additive effect by decreasing hepatic GHR expression and further suppression of IGF-I levels

in patients already under treatment with LA-SSAs, with or without PEGV. This hypothesis is supported by the observation that prolonged fasting, which might resemble the effect of SGLT2is, can normalize IGF-I levels completely in patients with acromegaly [12]. LA-SSAs bind to somatostatin receptors mainly subtypes 2 (sst2) and 5 (sst5) that are expressed on somatotrophic cells, leading directly to GH suppression and subsequently to decreased hepatic IGF-I production. These receptors are expressed in many other tissues including pancreatic islets cells, where LA-SSAs exert their effect through sst2 receptors expressed mainly on pancreatic  $\alpha$  cells and sst5 expressed mainly on  $\beta$  cells, inducing decreased glucagon and insulin secretion and deregulation of carbohydrate metabolism [13].

This negative effect is pronounced with PAS-LAR, which acts mainly on sst5 receptors. It is noteworthy that exacerbation of hyperglycemia in acromegaly represents one of the most frequent side effects that require initiation or intensification of antidiabetic therapy and sometimes discontinuation of PAS-LAR treatment [4].

Based on the above data, a reciprocal positive interaction is achieved with SGLT2is in combination with LA-SSAs and PEGV in this group of patients. On the one hand, SGLT2i attenuate the hyperglycemic effect induced by decreased insulin secretion due to LA-SSA therapy; on the other hand, LA-SSAs in combination with PEGV attenuate the hyperglucagonemia and enhanced lipolysis induced by SGLT2is. Moreover, PEGV via peripheral (extrahepatic) suppression of GHR in different tissues decreases lipid oxidation [14]. These mechanisms of action are supposed to minimize the appearance of EuDKA.

It is worthy of mention that SGLT2is promote weight reduction by inducing

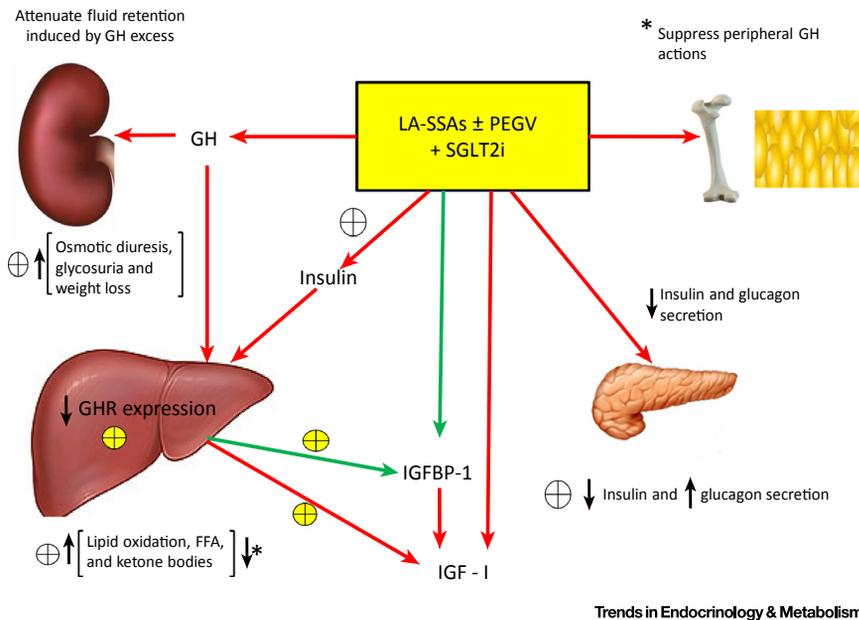
glycosuria and osmotic diuresis, which might be beneficial for patients with acromegaly and diabetes (Figure 1).

### When to Consider This Novel Class for Patients with Acromegaly and Diabetes?

SGLT2i can be recommended for the management of uncontrolled diabetes in the following category of patients with acromegaly. First, patients already under treatment with PEGV monotherapy or in combination with LA-SSAs. Treatment with SGLT2is in this category can be initiated after metformin monotherapy, or metformin in combination with dipeptidyl peptidase inhibitors (DPP-4is) or GLP-1Rc agonists. Second, patients with acromegaly under treatment who were previously diagnosed with T2DM. Third, PAS-LAR-induced new-onset diabetes as monotherapy or in combination with PEGV. Fourth, patients with T2DM with acromegaly achieved control after surgery only or with medical therapy.

Incretin-based therapy, such as DPP-4is and GLP-1Rc agonists, is currently used in this group of patients [15]. However, other classes of agents such as sulphonylureas, glinids, and thiazolidindiones are less attractive due to their known adverse events such as weight gain, hypoglycemia, and water retention. Treatment with SGLT2is is contraindicated in patients with acromegaly with T1DM and in patients with secondary diabetes due to unrecognized acromegaly. In this last group, severe hyperglycemia with DKA could be the first manifestation of acromegaly, thus initiation of insulin is mandatory. Additional agents might be considered after surgical intervention.

Precautions should be taken in patients with long duration of diabetes and acromegaly. Treatment with SGLT2is might be considered in this last category after



**Figure 1.** Schematic Illustration of Known Mechanisms of Action of LA-SSA ± PEGV, Known/Possible Mode of Action of SGLT2is in Patients with Acromegaly and Diabetes. Red arrows indicate inhibitory effects of LA-SSAs ± PEGV; green arrows indicate stimulatory effects LA-SSAs; open circles indicate known effects of SGLT2is; yellow circles indicate possible enhanced effect of SGLT2i; \*Effects induced by PEGV. Abbreviations: GH, growth hormone; GHR, GH receptor; IGF-I, insulin-like growth factor I; IGFBP-1, IGF binding protein 1; LA-SSA, long-acting somatostatin analog; PEGV, pegvisomant; SGLT2i, sodium glucose cotransporter inhibitor.

laboratory evaluation for  $\beta$  cell reserve including C-peptide levels and islets cell antibodies for those with suspected LADA. Insulin discontinuation is not recommended in patients treated with high-dose insulin, although insulin dose reduction should be considered after administering other agents including SGLT2is.

### Concluding Remarks and Future Perspectives

SGLT2is represent a novel class used for patients with T2DM. However, no published recommendations exist regarding their use for patients with acromegaly and diabetes, despite their unique mode of action by inducing glycosuria, osmotic diuresis, and weight loss, and their cardiovascular safety and superiority, which are favorable effects for this group of patients.

Furthermore, the hypoinsulinemic effect of SGLT2is is unique among antidiabetic agents, and it is hypothesized that this effect might be beneficial for patients with diabetes and acromegaly. EuDKA might constitute a barrier for many endocrinologists for initiating such a novel therapy, which is true for patients with undiagnosed acromegaly. However, in patients already under treatment, this complication seems to be as rare as in patients with T2DM. These data deserve further investigation and might urge clinicians, researchers, and pharmaceutical industries to perform clinical and basic science studies in order to prove or not this perspective.

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