Sodium Glucose Cotransporter 2 Inhibitors Treatment in Acromegalic Patients with Diabetes - A Case Series and Literature Review

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Abstract

Purpose

Diabetes mellitus (DM) represents one of the most frequent comorbidities in patients with acromegaly. Sodium glucose cotransporter 2 inhibitors (SGLT2i) represent an important class for diabetes management. However, limited data is reported regarding the use of this class in patients with acromegaly and diabetes.

Methods

Reporting data regarding patients with acromegaly and diabetes under treatment with SGLT2i.

Results

34 acromegalic patients with diabetes were identified. Treatment with SGLT2i was documented in nine patients, out of them 5 females and 4 males with a mean age (SD) of 61±12 yr. The mean (SD) duration of treatment with SGLT2i was 27.5±7.3 months. Mean HbA1c before and after SGLT2i initiation was 8.1±1.1% and 7.0±0.9% respectively. Mean IGF-1 level (SD) before SGLT2i initiation was 177±68 ng/mL and the mean GH level (SD) was 0.7±0.5 µg/L. All nine patients are still under treatment with SGLT2i and none of them had reported any adverse reaction related to SGLT2i.

Conclusions

The present article provides us for the first time with new data regarding the use of SGLT2i among acromegalic patients with diabetes.

Introduction

Acromegaly is a chronic disease generally caused by a GH-secreting pituitary adenoma [1]. GH excess causes insulin resistance and impair β cell function, predisposing a large number of patients with acromegaly to develop DM that represents one of the most frequent comorbidities in patients with acromegaly [2]. Treatment of diabetes has been revolutionized since the introduction of SGLT2i [3]. This important class with a unique mode of action is widely used in type 2 diabetes mellitus (T2DM) and recently was approved for patients with heart failure with reduced ejection fraction and for patients with chronic kidney disease (CKD) without diabetes [4, 5].

DKA is known as a rare serious acute complication of DM, often occurs as a result of profound insulin deficiency in poorly controlled type 1 diabetes and in patients with T2DM. Potential precipitating factors for DKA are multiple including acute illness, infection and surgical stress [8]. Euglycemic DKA has been recognized as a rare complication associated with the use of SGLT2i in patients with T2DM [9]. This class of agents increases plasma ketone levels through enhanced fat oxidation and augments synthesis as a result of increased glucagon to insulin ratio. Moreover, Glocosuria results in decreased insulin secretion, which is followed by decreased paracrine insulin inhibition of glucagon secretion. The later effect is further augmented by decreased alpha cell glucose uptake as a result from SGLT2 inhibition [10, 11]. Furthermore, a decrease in ketones elimination occurs during SGLT2i [12].

The excess GH in patients with active acromegaly increases lipolysis and ketone bodies production, predisposing this group of patients to develop DKA. For patients with unrecognized, active acromegaly with diabetes, treatment with SGLT2i increases the tendency for DKA and Euglycemic DKA development particularly in patients with insulin deficiency [7].

For Patient with uncontrolled acromegaly, different medical treatment modalities are available and include first- and second-generation somatostatin analogues (SSAs), Dopamine agonists and the GH-receptor (GHR) antagonist. It is well known that first generation SSAs have a marginal negative clinical impact on glucose homeostasis control in acromegaly, while hyperglycemia related adverse events were more common with second generation SSAs [13, 14]. PEGV is a GHR competitive antagonist. Compared to SSAs treatment, PEGV improves glycemic control among patients with acromegaly and diabetes beyond IGF-1 control. It has been shown to improve peripheral and hepatic insulin sensitivity in acromegaly [15]. Therefore, PEGV as monotherapy or in combination with SSAs represents a favorable treatment option in patients with partially controlled or resistant acromegaly to SSAs in the presence of diabetes or worsening hyperglycemia [16].

limited data is reported in the literature regarding the use of SGLT2i among patients with already diagnosed acromegaly and diabetes.

Methods

In the present case series, data was collected using electronic computerized registry at Clalit Medical Health (CMH) Services from Western Galilee and Haifa district between the years 2000–2020 and during patients visits for routine follow up in our department. Charts of patients with acromegaly and diabetes were reviewed thoroughly for current and previous anti-diabetic and acromegaly medications. Notably, that electronic computerized files enable health care practitioners to follow the monthly treatment dispensing and reported drug side effects. Laboratory results for fasting plasm glucose (FPG), hemoglobin A1c, IGF-1 and GH were reported before SGLT2i administration. Actual hemoglobin A1c and Body mass index (BMI) were documented while the patients were still taking SGLT2i treatment. This study was approved by The Ethics (Helsinki) Committee at the Meir Medical Center.
Results

We had identified 34 patients diagnosed with acromegaly and diabetes. Of these, nine patients, 5 females and 4 males, were under treatment with SGLT-2i as part of their anti-diabetic regimen. The mean age (SD) was 61 ± 12 years (range, 41 to 80 years) and the median duration (SD) of SGLT2i treatment was 27.5 ± 7.3 months (range, 13 to 36 months). Mean HbA1c before SGLT-2i initiation was 8.1 ± 1.1% and the actual mean HbA1c while the patients were still taking SGLT2i was 7.0 ± 0.9% respectively with a mean BMI 32 ± 3.3 kg/m².

The mean IGF-1 (SD) before SGLT-2i initiation was 177 ± 68 ng/ml and the mean GH level was (SD) 0.7 ± 0.5 µg/L. IGF-1 levels were within normal range in 8 out of 9 patients. In one patient IGF-1 was moderately high 338 ng/mL (normal range is 74–236 ng/mL) and the GH was 1.4 µg/L. There were no adverse reactions related to SGLT-2i reported (Table 1, 2).

Table 1

| Patients with acromegaly and Diabetes, n | 34 |
|----------------------------------------|----|
| Patients with SGLT-2i treatment, n     | 9  |
| Age of patients with SGLT-2i treatment, mean ± SD | 61 ± 12 |
| Range (years)                          | 41–80 |
| Female/Male                            | 5:4 |
| Duration of diabetes, mean ± SD        | 9.3 ± 5.8 |
| Range (years)                          | 3–17 |
| Duration of SGLT-2i treatment (mean) ± SD | 27.5 ± 7.3 |
| Range (months)                         | 13–36 |
| FPG before SGLT2i treatment, mean ± SD | 142 ± 22 |
| HbA1c before SGLT2i treatment, mean ± SD | 8.1 ± 1.1 |
| Current HbA1c (%) under SGLT2i treatment, mean ± SD | 7.0 ± 0.9 |
| BMI kg/m², mean ± SD                   | 32 ± 3.3 |
| GH (µg/L) ± SD                         | 0.7 ± 0.5 |
| IGF-1 (ng/mL) ± SD                     | 177 ± 68 |

Table 2 Characteristics of Patients with acromegaly and diabetes under treatment with SGLT-2 inhibitors
| Age (years) | Sex | Tumour Diameter (mm) | Acromegaly Treatment modalities | GH* µg/L | IGF-1* ng/mL | FPG* mg/dL | HbA1c% | BMI Kg/m² | Diabetes Diagnosis (years) | Diabetes Treatment |
|------------|-----|----------------------|---------------------------------|---------|-------------|-----------|------|---------|--------------------------|-----------------|
| 1          | 66  | >10 mm               | TSS LA-SSA                      | 1.6     | 144         | 137       | 7     | 27      | 4                        | Dapagliozin/     |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin XR     |
|            |     |                      |                                 |         |             |           |       |         |                          | Glimepiride      |
|            |     |                      |                                 |         |             |           |       |         |                          | Pioglitazone     |
| 2          | 44  | 32 mm                | TSS RTx PAS-LAR PEGV            | 1.5     | 338         | 151       | 8.9   | 6.9     | 31                       | Empagliflozin/   |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin       |
|            |     |                      |                                 |         |             |           |       |         |                          | Ins. Glargin     |
|            |     |                      |                                 |         |             |           |       |         |                          | Ins. Aspartide  |
| 3          | 68  | < 10 mm              | TSS                             | 0.4     | 175         | 137       | 8.7   | 7.3     | 34                       | Empagliflozin    |
|            |     |                      |                                 |         |             |           |       |         |                          | Liraglutide      |
|            |     |                      |                                 |         |             |           |       |         |                          | Ins. Degludec    |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin       |
| 4          | 54  | >10 mm               | TSS LA-SSA                      | 0.3     | 215         | 119       | 7.2   | 6.7     | 27                       | Dapagliozin/     |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin XR     |
| 5          | 5   | 13 mm                | TSS, LA-SSA, PEGV, CAB          | 0.1     | 117         | 115       | 6.7   | 6.2     | 34                       | Empagliflozin/   |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin       |
| 6          | 65  | 7                    | TSS                             | 0.1     | 167         | 184       | 8.3   | 5.9     | 37                       | Empagliflozin    |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin       |
| 7          | 76  | 16                   | NA                              | 0.4     | NA          | 150       | 9.8   | 7.9     | 35                       | Empagliflozin    |
|            |     |                      |                                 |         |             |           |       |         |                          | Dulaglutide     |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin       |
| 8          | 81  | 18                   | NA                              | 1.1     | 146         | 168       | 9.6   | 9.2     | 31                       | Dapagliozin/     |
|            |     |                      |                                 |         |             |           |       |         |                          | Metformin XR,   |
|            |     |                      |                                 |         |             |           |       |         |                          | Ideg/Lira       |
| 9          | 54  | 32                   | TSS PAS-LAR                     | 0.6     | 116         | 117       | 6.8   | 6.7     | 29                       | Empagliflozin    |
|            |     |                      |                                 |         |             |           |       |         |                          | 2               |

*IGF-1, GH, HbA1c and FPG levels before SGLT-2 inhibitor treatment.

Abbreviations: TSS; Transsphenoidal, RTx; Radiotherapy, LA-SSA; Long-acting somatostatin analog, PAS-LAR, pasireotide long-acting release, PEGV, Pegvisomant, CAB, Cabergoline

**Discussion**

The results of this case series provide us for the first time with a new data regarding diabetes management in acromegaly, focusing on the use of SGLT-2 class. SGLT2i represent an important class and are widely used in the management of diabetes. Previously reported data of increased risk of DKA in patients with unrecognized active acromegaly has decreased the tendency of clinicians to use this important anti-diabetic class even among patients with already diagnosed and controlled acromegaly [7].

A PubMed search has been conducted using the terms ‘acromegaly and ketosis’, ‘acromegaly and diabetic ketoacidosis’, ‘acromegaly and sodium glucose cotransporter 2 inhibitors. Our search focused also on pituitary tumor size, recognized vs. unrecognized acromegaly and disease activity reflected by IGF-1 and GH levels.

We had identified 27 acromegalic patients presented with DKA [17, 7, 18–34]. For the majority of the cases (25 out of 27) DKA was the initial presentation of unrecognized active acromegaly in patients harboring macroadenoma with significantly high levels of GH and IGF-1. Interestingly, in our search we did not identify any reported case presented with DKA in association with microadenoma (Table 3). Worthy to mention that DKA was reported in two cases with already diagnosed acromegaly. In the first case, a high dose glucocorticoid administration was considered a precipitating factor for DKA in the presence of consistently elevated GH levels after a partial adenoma resection [19]. In the second case, a significant residual pituitary tumor was not removed, reflecting persistently elevated GH excess [20].
should be considered as well. For patients with suspected latent autoimmune diabetes of adults (LADA) islets cell antibodies can be considered according to blood glucose levels in patients with insulin treatment. Laboratory evaluation for 2i in the above categories can be used with metformin, as monotherapy or in combination with DPP-4 inhibitors or GLP-1 receptor agonists. A dose reduction or PEGV either as monotherapy or in combination. Third; PAS-LAR controlled acromegalic patients with worsening hyperglycemia or new onset diabetes. SGLT-2i diagnosed T2DM and controlled acromegaly after surgery. Second; patients with diabetes and controlled acromegaly under treatment with long acting SSAs previous insulin based anti-diabetic regimen. Under these modalities of treatment, the patient achieved normalized IGF-1 and diabetes control.

For patient nr. 2 due to partially controlled disease with a high GH level (1.4 µg/L) and a high IGF-1 (338 ng/mL; age- and sex- specific reference range, 74–236 ng/mL) the patient was on PAS-LAR monotherapy. Due to hyperglycemia and uncontrolled diabetes treatment with SGLT2 was added to his previous insulin based anti-diabetic regimen. Under these modalities of treatment, the patient achieved normalized IGF-1 and diabetes control.

Treatment with SGLT-2i could be considered for diabetes management in the following categories of patients with acromegaly: first; patients with previously diagnosed T2DM and controlled acromegaly after surgery. Second; patients with diabetes and controlled acromegaly under treatment with long acting SSAs or PEGV either as monotherapy or in combination. Third; PAS-LAR controlled acromegalic patients with worsening hyperglycemia or new onset diabetes. SGLT-2i in the above categories can be used with metformin, as monotherapy or in combination with DPP-4 inhibitors or GLP-1 receptor agonists. A dose reduction can be considered according to blood glucose levels in patients with insulin treatment. Laboratory evaluation for β cell reserve including C-peptide level is recommended in patients with long duration of diabetes. For patients with suspected latent autoimmune diabetes of adults (LADA) islets cell antibodies should be considered as well.

Table 3

| Authors             | Year | cases | Age | Sex | Max. tumor size (mm) | GH ng/ml | IGF1 ng/ml | Initial | Presentation   |
|---------------------|------|-------|-----|-----|----------------------|----------|------------|---------|---------------|
| Ocampo P et al. [17]| 2018 | 1     | 38  | M   | 22                   | 192      | 393        | DKA    |               |
| Biil S et al. [7]   | 2017 | 1     | 52  | M   | > 10                 | 18.6     | 849        | DKA    |               |
| Herrero Ruiz A et al. [18] | 2017 | 1     | 35  | F   | 20                   | 48.1     | 702        | DKA    |               |
| Ekinci El et al. [19]| 2017 | 1     | 18  | F   | > 10                 | 246.5    | 1009       | Aenonrea|               |
| Inaba H et al. [20] | 2016 | 1     | 43  | M   | 52                   | 6.2      | 800        | Hemianopsia |               |
| Yoshida N et al. [21]| 2013 | 9     | 60  | M   | NA                   | 35       | NA         | DKA    |               |
| Patell RD et al. [22]| 2013 | 1     | 45  | M   | 16                   | NA       | 1031       | DKA    |               |
| Hsiao PJ et al. [23]| 2013 | 1     | 49  | M   | 21                   | 59.9     | 839        | DKA    |               |
| Arakaki R et al. [24]| 2012 | 1     | 23  | M   | 24                   | 115      | 1118       | DKA    |               |
| Mewawalla P et al. [25]| 2012 | 1     | 54  | M   | 20                   | 29.1     | 921        | DKA    |               |
| Chowdhury TA et al. [26]| 2009 | 1     | 31  | F   | > 10                 | 250      | 1001       | DKA    |               |
| Chen YL et al. [27]| 2007 | 1     | 57  | M   | 17                   | 49.5     | 602        | DKA    |               |
| Lakhotia M et al. [28]| 2007 | 1     | 22  | M   | > 10                 | 9.7      | NA         | DKA    |               |
| Erem C et al. [29]| 2006 | 1     | 37  | M   | 22                   | 124      | 776        | DKA    |               |
| Kopff B et al. [30]| 2001 | 1     | 37  | M   | 25                   | 42.2     | 1575       | DKA    |               |
| Westphal SA et al. [31]| 2000 | 1     | 37  | M   | 15                   | 27.7     | NA         | DKA    |               |
| Szeto CC et al. [32]| 1997 | 1     | 22  | F   | 17                   | 39       | NA         | DKA    |               |
| Katz JR et al. [33]| 1996 | 1     | 40  | M   | > 10                 | 37.1     | NA         | DKA    |               |
| Vidal Cortada J et al. [34]| 1995 | 1     | 20  | F   | > 10                 | 560      | NA         | DKA    |               |

A rapid onset DKA was reported in one patient with unrecognized acromegaly after SGLT2 inhibitor initiation with elevated GH concentration (18.6 mg/L) and high level of IGF-1 (111 nmol/L; age- and sex- specific reference range, 7 to 31 nmol/L) harboring macroadenoma [7].

In the study of Yoshida et al [21], DKA was reported as an initial manifestation in nine patients with unrecognized, active acromegaly with marked elevation in mean GH (SD) levels 155 ± 203 ng/ml (range, 11–606 ng/mL) and IGF-1(SD) levels 982 ± 98 ng/mL (range, 804–1082 ng/mL) (19), while in our case series, treatment with SGLT2i was initiated in nine patients with already recognized and treated acromegaly with a mean GH (SD) levels 0.7 ± 0.5 µg/L and IGF-1(SD) levels 155 ± 203 ng/ml (range, 11–606 ng/mL) while the patient was on PAS-LAR monotherapy. Due to hyperglycemia and uncontrolled diabetes treatment with SGLT2i was added to his previous insulin based anti-diabetic regimen. Under these modalities of treatment, the patient achieved normalized IGF-1 and diabetes control.

| Authors             | Year | cases | Age | Sex | Max. tumor size (mm) | GH ng/ml | IGF1 ng/ml | Initial | Presentation   |
|---------------------|------|-------|-----|-----|----------------------|----------|------------|---------|---------------|
| Patell RD et al. [22]| 2013 | 1     | 45  | M   | 16                   | NA       | 1031       | DKA    |               |
| Hsiao PJ et al. [23]| 2013 | 1     | 49  | M   | 21                   | 59.9     | 839        | DKA    |               |
| Arakaki R et al. [24]| 2012 | 1     | 23  | M   | 24                   | 115      | 1118       | DKA    |               |
| Mewawalla P et al. [25]| 2012 | 1     | 54  | M   | 20                   | 29.1     | 921        | DKA    |               |
| Chowdhury TA et al. [26]| 2009 | 1     | 31  | F   | > 10                 | 250      | 1001       | DKA    |               |
| Chen YL et al. [27]| 2007 | 1     | 57  | M   | 17                   | 49.5     | 602        | DKA    |               |
| Lakhotia M et al. [28]| 2007 | 1     | 22  | M   | > 10                 | 9.7      | NA         | DKA    |               |
| Erem C et al. [29]| 2006 | 1     | 37  | M   | 22                   | 124      | 776        | DKA    |               |
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| Szeto CC et al. [32]| 1997 | 1     | 22  | F   | 17                   | 39       | NA         | DKA    |               |
| Katz JR et al. [33]| 1996 | 1     | 40  | M   | > 10                 | 37.1     | NA         | DKA    |               |
| Vidal Cortada J et al. [34]| 1995 | 1     | 20  | F   | > 10                 | 560      | NA         | DKA    |               |

A rapid onset DKA was reported in one patient with unrecognized acromegaly after SGLT2 inhibitor initiation with elevated GH concentration (18.6 mg/L) and high level of IGF-1 (111 nmol/L; age- and sex- specific reference range, 7 to 31 nmol/L) harboring macroadenoma [7].
Despite the small number of patients reported here, the above nine patients have been treated successfully with different modalities for both acromegaly and diabetes including the use of SGLT2i class.

Conclusions

The current case series report provides us for the first time with new data regarding the use of SGLT2i among patients with acromegaly and diabetes. Reviewing the literature, DKA has been reported in patients with undiagnosed active acromegaly harboring macroadenoma. In patients with diabetes with already diagnosed and treated acromegaly, SGLT-2i could be considered for this group of patients. However, further large clinical research is required in this field.

Declarations

Financial Support
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Compliance with ethical standards

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure Summary: The authors have nothing to disclose.

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