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The SGLT-1/SGLT-2 dual inhibitor canagliflozin has positive effects on glucose trends, targets and variability in late dumping syndrome following gastrectomy: A case report

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ABSTRACT

Background: Late dumping syndrome (LDS) refers to reactive hyperinsulinemic hypoglycemia episodes that occur one to 3 h following a high-carbohydrate meal in persons who have had gastric surgery. Dietary adjustments (such as regular composite meals containing lipids, protein, and carbohydrates with a low glycemic index) are effective in treating the majority of LDS patients; however, pharmaceutical interventions are required in some cases.

Case presentation: We describe the case of a 60-year-old woman with type 2 diabetes (T2DM) who developed late dumping syndrome symptoms following a gastric cancer gastrectomy. Both the 75-g oral glucose tolerance test (OGTT) and the mixed-meal tolerance test (MMTT) revealed reactive hyperinsulinemic hypoglycemia. We began therapy with canagliflozin, a sodium glucose-cotransporter (SGLT) inhibitor 300 mg before lunch after realizing that dietary changes were insufficient in reducing the occurrence of symptomatic hypoglycemic episodes. We repeated the OGTT after treatment, and the results showed still the presence of symptomatic hypoglycemia without significant differences in peak insulin values compared to the OGTT performed before treatment. Instead, the MMT showed a small, flattened insulin response without any hypoglycemic episodes. Furthermore, improvements were observed in glucose trends/targets as demonstrated by time in (TIR), above (TAR) and below (TBR) range and glucose variability (e.g. coefficient of variation) based on data collected from Flash Glucose Monitoring (FGM) before and during canagliflozin therapy.

Conclusion: The rapid transit of inadequately digested chyme from the stomach into the small intestine is one of the most important pathophysiological processes in LDS. Canagliflozin, unlike other molecules in the same family, inhibits intestine SGLT-1. By delaying glucose absorption at that level, it may reduce postprandial glucose and insulin rises. Our case report, however, demonstrates that the effect of canagliflozin on glucose homeostasis is determined by appropriate dietary habits, which seem to be critical for successfully reducing symptoms related to reactive hyperinsulinemic hypoglycemia following a gastric bypass surgery.

1. Introduction

Dumping syndrome is a clinical condition that occurs in patients who have undergone gastric surgery. Its severity is correlated with the extent of gastric surgery. Surgical etiologies include gastrojejunostomy, antrectomy, pylorectomy, pyloroplasty, esophagectomy, vagotomy, Roux-en-Y bypass, and Nissen fundoplication [1,2]. The quick passage of hyperosmolar and poorly digested chyme from the stomach into the small intestine is the main cause of this condition [3,4], which is responsible of symptoms like nausea, bloating, abdominal cramps, diarrhea and sudden blood sugar changes. Specifically, reactive hyperinsulinemic hypoglycemia (e.g. late dumping syndrome - LDS) usually occurs 1–3 hours after a high-carbohydrate meal [5–7].

Most cases of LDS are successfully treated with dietary adjustments: meals should be divided so that smaller portions of food are consumed with greater frequency, and liquids should not be consumed until 30

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minutes after each meal. Additionally, simple sugars and milk products should be avoided and protein and fat calories should be increased to compensate for a decreased carbohydrate intake. Fiber-rich food is encouraged as it promotes a longer transit time in the bowel [8]. In patients who continue to demonstrate symptoms despite dietary modifications, drug therapy may be considered. Among others, octreotide, a somatostatin analog which can determine delayed gastric emptying, prolonged small intestine transit time and decreased insulin release, and acarbose, a competitive inhibitor of intestinal brush border α-glycosidase, should be mentioned [9,10].

The pathophysiological mechanism of LDS-associated symptoms is still not completely elucidated. Recent studies suggest an up-regulation of the intestinal sodium-glucose transporter-1 (SGLT-1) in an effort to prevent malabsorption of carbohydrates. In this context, the rapid absorption of carbohydrates exacerbates the insulin response mediated by glucose [11] which is thought to be one of the key mechanisms underlying the large glycemic excursions observed in patients following a gastrectomy. Indeed, a potential novel therapeutic option for treating patients suffering from late dumping syndrome is to target this metabolic pathway. However, there are very few specific studies examining the use of SGLT-1/SGLT-2 inhibitors in patients experiencing reactive hyperinsulinemic hypoglycemia following gastric surgery [12–14].

2. Case report

We report the case of a 60-year-old woman with type 2 diabetes (T2DM) who frequently experienced postprandial hypoglycemic episodes. In 2021 she underwent subtotal gastrectomy with gastro-jejunal anastomosis for gastric cancer. She began to exhibit LDS symptoms three months after the surgery, including sweating, tachycardia, confusion, anxiety, and weakness after meals, especially those high in carbohydrates. During these episodes, which typically relieved after the assumption of a snack, she detected low capillary glucose concentration (values often lower than 30 mg/dl) with her own glucometer, thus satisfying the diagnostic criteria of the Whipple's triad [15]. Other causes of hypoglycemia were excluded (alcohol intake, iatrogenic hypoglycemia, Hirata Syndrome, deficiencies of counter-regulatory hormones) [16,17] through careful anamnestic assessment as well as specific laboratory assays (insulin, c-peptide, insulin autoantibodies, IGF-1 and cortisol assays). Apart from her anamnestic cancer and T2DM (the latter diagnosed by means of two random plasma glucose values higher than 200 mg/dl), the patient did not suffer from any other acute or chronic disease based on both blood tests (normal liver and kidney function, normal blood count and low *C*-reactive protein levels) and clinical examination. Her glycated hemoglobin A1c was 5.5% (normal range 4.0–5.7%), which could have been influenced by the high number of hypoglycemic episodes experienced by the patient.

The patient had reactive hyperinsulinemic hypoglycemia, as evidenced by her blood glucose of 46 mg/dl 120 minutes following a 75-g oral glucose tolerance test (OGTT) with an insulin peak of 275 mU/l at 60 minutes (Fig. 1A).

Similarly, the mixed-meal tolerance test (MMTT - composed of 495 Kcal, 64% carbohydrates, 27% fat and 9% protein) was characterized by the occurrence of precocious hyperinsulinemia (211 mU/l at 30 minutes) responsible for a glucose nadir of 59 mg/dl at 240' (Fig. 1B).

Initially, we recommended small, frequent meals containing complex carbohydrates combined with fiber, protein, and healthy fats, while advising against high-glycemic index sugars. Moreover, we recommended frequent follow-up appointments with a registered dietitian.

The patient also received a Flash Glucose Monitoring (FGM, Freestyle libre 2) system at the same time, enabling her to continuously monitor glucose trends in interstitial fluid and set appropriate predictive alarms for impending hypoglycemia.

Three months later, as the patient's symptoms of hypoglycemia and rapid glycemic excursions persisted, canagliflozin, a sodium glucose-cotransporter (SGLT) receptor inhibitor, 300 mg was started before lunch.

Following a week of treatment, we repeated the prolonged OGTT (Fig. 2A), which revealed no substantial differences in peak insulin values and symptomatic hypoglycemia, and the MMTT (Fig. 2B), which differed from the previous observation conducted prior to canagliflozin treatment, revealing a small and flattened response and the absence of hypoglycemic episodes.

Further analysis of two weeks FGM data collected prior to (Fig. 3A) and during (Fig. 3B) canagliflozin therapy revealed an improvement in both glucose trends/targets as demonstrated by time in (TIR, 95% vs.

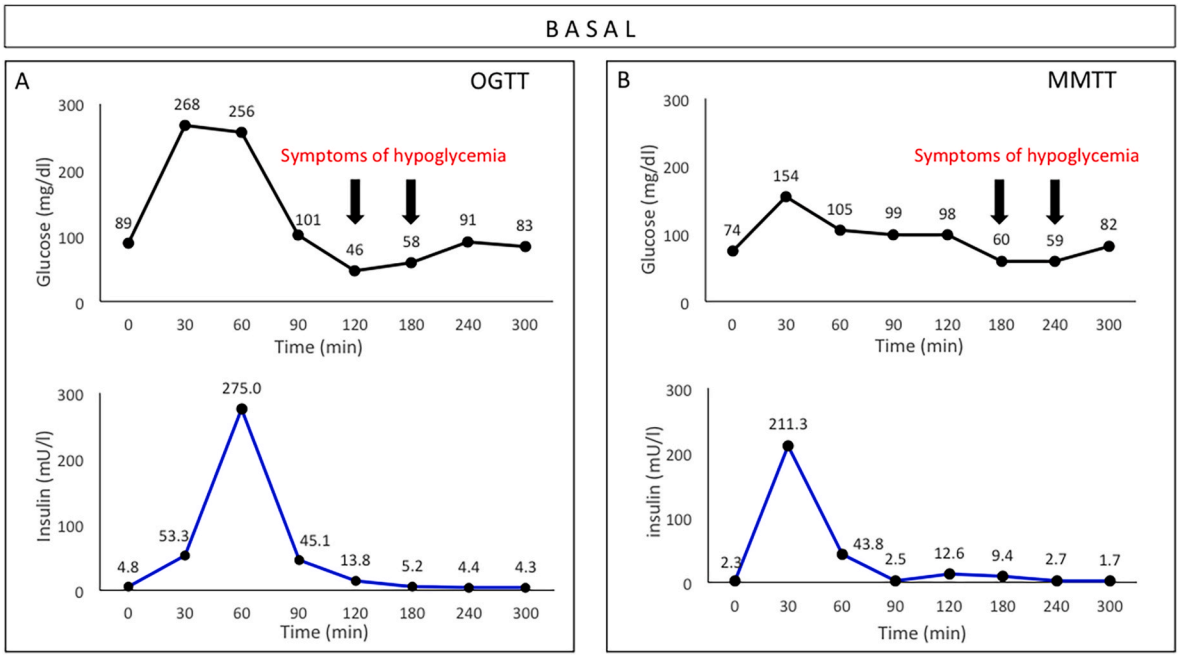

Fig. 1. Glucose (black lines) and insulin (blue lines) values at OGTT (A) and MMTT (B) in the patient in basal conditions. Abbreviation: OGTT, oral glucose tolerance test; MMTT, mixed meal tolerance test. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

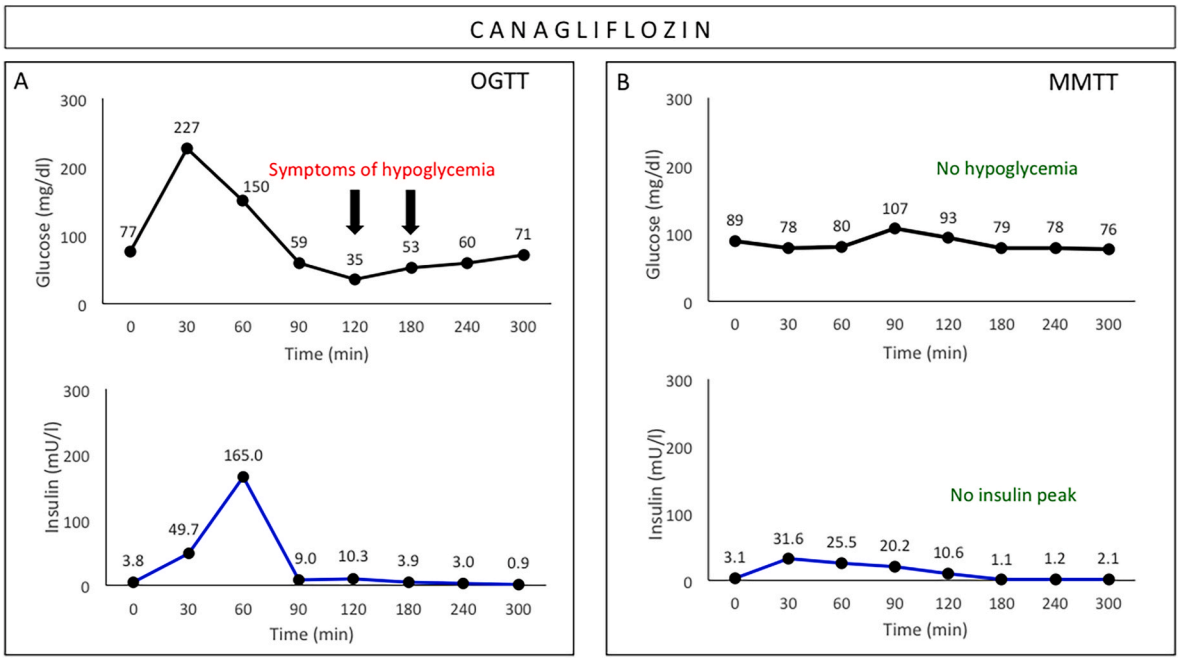

Fig. 2. Effect of canagliflozin on glucose (black lines) and insulin (blue lines) values at OGTT (A) and MMTT (B). Abbreviation: OGTT, oral glucose tolerance test; MMTT, mixed meal tolerance test. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

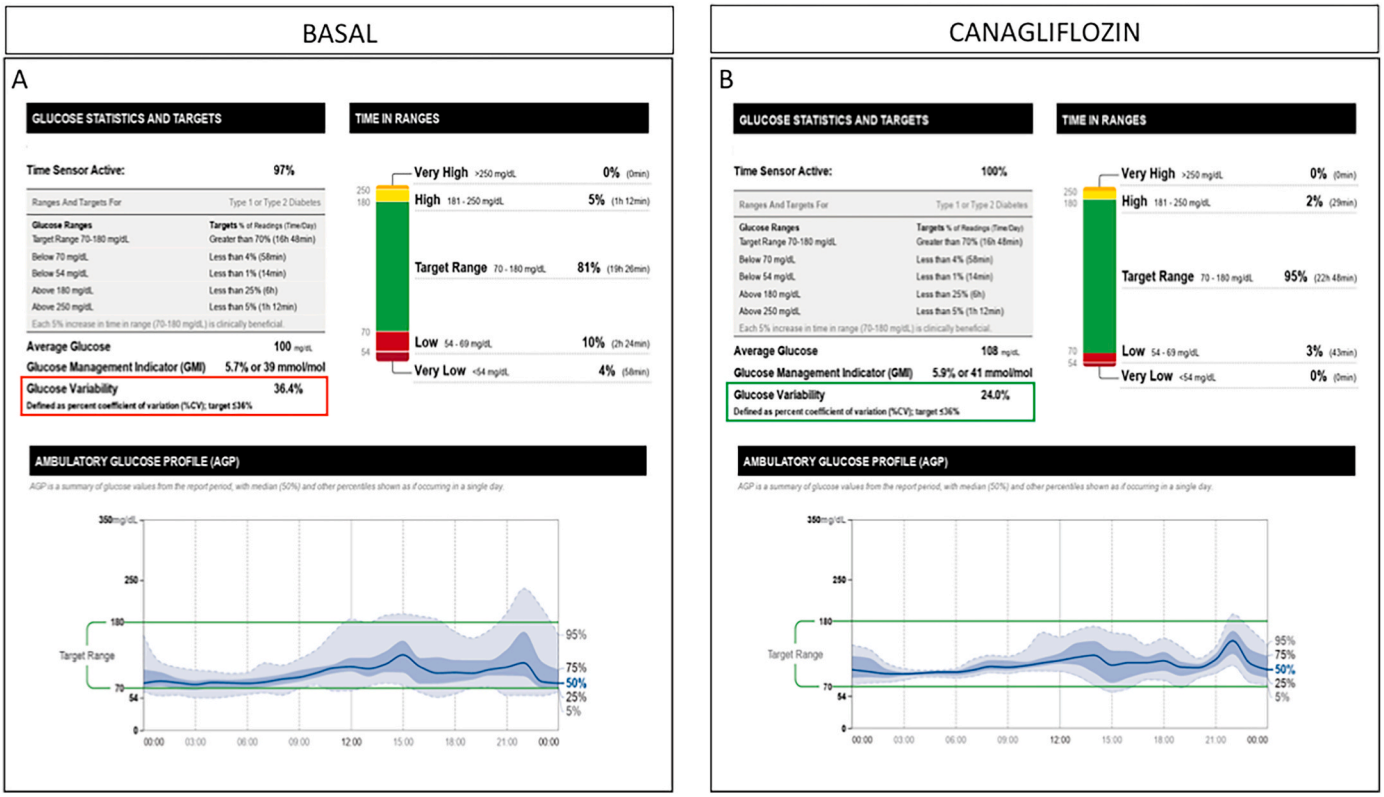

Fig. 3. Fourteen days glucose statistics (targets and variability), time in ranges and ambulatory glucose profiles (AGP) under basal conditions (A) and on canagliflozin (B).

81%), above (TAR, 2% vs. 5%) and below (TBR, 3% vs. 14%) range and, interestingly, in the coefficient of variation (CV, 24.0% vs. 36.4%), a well-characterized parameter of intra-day glycemic variability [18,19].

Finally, treatment satisfaction was evaluated using an Italian validated tool (the Diabetes Treatment Satisfaction Questionnaire - DTSQ) [20,21], which was administered both before and during canagliflozin treatment. In this regard, Q3 of the questionnaire, which assesses the perceived risk of hypoglycemia, changed from 6 to 1, while the remaining items remained stable. When asked, the patient confirmed a higher level of quality of life and general well-being following the start

of canagliflozin therapy.

3. Discussion

To our knowledge, our case report is the first that thoroughly evaluates the impact of canagliflozin on the hyperinsulinemic response and its closely related hypoglycemia, and the novel sensor-derived parameters of glucose control (e.g., trends/targets/variability) in a patient with T2DM who underwent subtotal gastrectomy for gastric cancer using two validated tolerance tests (e.g., OGTT and MMTT).

Canagliflozin, in addition to inhibiting SGLT-2, inhibits SGLT-1 expressed in the brush border of the small intestine at higher clinical doses (>200 mg) [22]. As a result, unlike other molecules in the same family, canagliflozin may reduce postprandial glucose and insulin spikes by delaying intestinal glucose absorption.

There are currently few studies involving subjects who have had gastrointestinal surgery.

In a recent randomized controlled crossover trial with ten patients, Martinussen et al. demonstrated that high canagliflozin dosages (e.g., 600 mg daily) can reduce postprandial blood glucose levels along with glucagon-like peptide 1 (GLP-1) peaks, indicating that intestinal glucose absorption through SGLT-1 can determine an increased incretin response following glucose ingestion [14].

Ciudin et al. then investigated the effect of 300 mg canagliflozin administration by evaluating 21 patients undergoing Roux-en-Y bypass with a 100-g OGTT performed at baseline and after 2 weeks of canagliflozin treatment. The authors demonstrated that the OGTT after canagliflozin treatment was characterized by a significant reduction in plasma glucose and insulin levels, as well as a significant reduction in the rate of hypoglycemia [23].

Although our case report's findings are preliminary, they highlight the potential importance of SGLT-1 inhibition in a patient experiencing hyperinsulinemic hypoglycemia after a gastrectomy by evaluating insulinemic and glucose trends in response to qualitatively distinct meals (e.g., OGTT and MMTT).

In our patient, the complete absence of hyperinsulinemic peak and, as a result, symptomatic hypoglycemia was obtained only by combining canagliflozin with a composite meal containing fats, protein, and carbohydrates at the same time (Fig. 2B). Conversely, even during pharmacological therapy, the sole administration of glucose resulted in hypoglycemic episodes (Fig. 2A). Although the pathophysiological mechanisms are not certain, we can hypothesize that both SGLT-1 overexpression and a defective incretin action in T2DM patients may play a role in determining these different clinical and biochemical responses [24,25]. Indeed, this phenomenon emphasizes the importance of nutritional intervention in the non-negligible number of patients suffering from post-surgery LDS.

Finally, our case study validates efficacy of canagliflozin on sensor-related indicators of glucose trends/targets (with an average 101 min less time spent in hypoglycemia and the absence of values < 54 mg/dl during the therapy), and variability with less fear of hypoglycemia.

More research is required to confirm and clarify this promising therapeutic opportunity.

4. Conclusion

LDS is characterized by reactive hyperinsulinemic hypoglycemia occurring one to 3 h following a high-carbohydrate meal in persons who have had gastric surgery.

Canagliflozin, by delaying glucose absorption at intestinal level, may reduce postprandial glucose and insulin rises and, therefore, symptoms related to LDS. Our case report, however, demonstrates that glycometabolic achievements following pharmacological therapy are deeply linked to proper dietary habits, which seem to be crucial for successfully reducing post-gastrectomy LDS.

Ethics statement

The patient provided written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of this case report.

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CRediT authorship contribution statement

Andrea Tumminia: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **Ausilia Maria Lombardo:** Conceptualization, Data curation, Investigation, Validation. **Maria Luisa Arpi:** Conceptualization, Methodology, Supervision, Validation. **Roberto Baratta:** Conceptualization, Investigation, Methodology, Validation. **Daniela Leonardi:** Conceptualization, Data curation, Validation. **Ilenia Marturano:** Conceptualization, Methodology, Supervision. **Francesco Frasca:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation. **Damiano Gullo:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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