CASE REPORT

First Beneficial Use of Dapagliflozin for Treatment of Post-Bariatric Hypoglycemia: Case Report and Hypothesis

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Abstract

Background: Hypoglycemia is a significant complication of post-bariatric surgery. **Case history:** A 46 year old woman was referred for further management. She had had a Roux-en-Y gastric bypass surgery in 2012. She lost over 20 kilograms of weight. Pre-opertaively, a single HbA1c was borderline at 48 mmol/mol (6.5%) which improved to 41-44 mmol/mol. In November 2013, she started to experience symptoms suggestive of hypoglycemia. Dietary adjustments were advised and a trial of metformin and saxagliptin was given on basis of wide fluctuation of blood glucose with a remarkable early postprandial hyperglycemia followed by hypoglycemia. She stopped both medications due to gastrointestinal side effects. Renal and liver disease and hypoadrenalism were all excluded. We started her on increasing doses of Acarbose (an alpha glucosidase inhibitor) up to 100 mgs with each meal but she experienced minimal improvement in hypoglycemia. A a trial of Dapagliflozin, a sodium-glucose co-transporter 2 (SGLT 2) inhibitor, in a standard daily dose of 10 mgs in addition to Acarbose was offered to the patient (from 6th October 2015). The theoretical basis were explained to her and she consented verbally to this. Within 2 weeks, she experienced remarkable symptomatic improvement associated with reduction of both hyperglycemia and hypoglycemia documented on self-monitoring of blood glucose. The patient reduced Acarbose progressively to a complete cessation on her own accord. She remained well controlled solely on Dapagliflozin 10 mgs daily. The improvement is sustained for 12 months. The effect was further confirmed by 1 week off and one week on Dapagliflozin using flash glucose monitoring. **Conclusions:** This is the first report of a beneficial use of SGLT2 inhibition primarily for post-bariatric hypoglycemia. SGLT2 inhibitors may have a role in managing gastric bypass hypoglycemia.

Key words: Continuous glucose monitoring; Gastric bypass; Hypoglycemia; Dapagliflozin.

Introduction

Beyond the immediate complications of surgery, there are potential long-term consequences (1). Patient education stressing the need for rigorous lifelong adherence to nutritional supplementation therapy has been particularly emphasized and regular and meticulous long-term monitoring of nutrient status is essential (2).

One challenging and potentially life-threatening complication is post-bariatric hypoglycemia (3-5). The number of patients presenting with this has been increasing. Roux-en-Y gastric bypass (RYGB) being the type of surgery most commonly associated with the development of post-bariatric surgery hypoglycemia. Suggested management approaches involve empirical dietary adjustments, drug therapy and even surgical reversal (3-5).

The pathogenesis of this condition has not been completely established. However, several potential mechanisms of post bariatric hypoglycemia have been postulated. The same mechanisms responsible for diabetic remission after bariatric surgery seem to be responsible for the development of hypoglycemia which typically occurs 1-3 h after a meal and is concurrent with inappropriate hyperinsulinemia. These are probably related to increased secretion of the incretin hormones. Patients with post-RYGB hypoglycemia demonstrate prolonged elevations of these hormones compared to non-hypoglycemic post-RYGB patients. Nesidioblastosis has been identified in some patients with post-RYGB hypoglycemia and is likely due to the trophic effects of the incretin hormones on pancreatic islets. (3-5). In this case report, experience of a single patient with post bariatric hypoglycemia for whom a novel approach to management was employed is described.

Case history

A 46 year old woman was referred to the endocrine clinic in March 2015 for assessment and further management of symptoms suggestive of post-bariatric hypoglycemia. She had had RYGB in 2012. Post operatively she lost over 20 kg of weight (131 to 110 kg). Between July and November 2013, she complained from episodes of dizziness, shaking and other symptoms suggestive of hypoglycemia and confirmed by low blood glucose using glucometer down to 38 mg/dl and responding to intake of a sugary drinks. At least on one occasion, she fell and lost consciousness. She attended emergency departments and her own family doctor on several occasions for the same problems. She was seen by two endocrine firms previously who confirmed hypoglycemia on continuous glucose monitoring (CGM) (Figure 1)

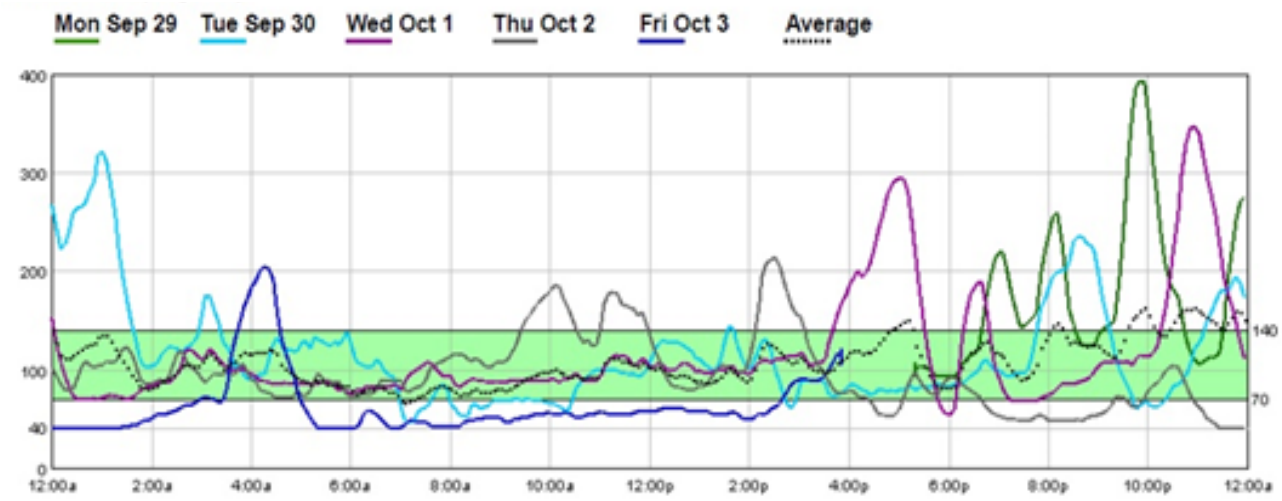

Figure 1. The initial documentation of hyperglycemia and hypoglycemia by a 5 day CGM recording on no treatment.

Table 1. Biochemical investigations in the early stages of presentation of postprandial hypoglycemia.

Parameters	Date (s)	Patients data (n)	Normal ranges/Comment
Serum Sodium	10.11.2013-29.9.2014	139-141 (3)	135-145mmol/l
Serum Potassium	10.11.2013-29.9.2014	3.8-4.3 (3)	3.4-5.1 mmol/l
Serum Creatinine	10.11.2013-29.9.2014	55-70 (4)	45-84 micromol/l
Estimated GFR	4.2.2014-29.9.2014	90, 108 (2)	Ml/min/1.73m^2
Serum Urea	10.11.2013-29.9.2014	2.5-3.1 (3)	3.1-8.3 mmol/l
Plasma Albumin	10.11.2013-29.9.2014	32-39 (3)	35-52 g/l
Serum Bilirubin (Total)	10.11.2013-29.9.2014	4.2-9.1 (3)	<21.0 micromol/l
Serum Bilirubin (Direct)	23.4.2013-29.9.2014	1.7, 2.1 (2)	<5.0 micromol/l
Serum AST	10.11.2013-29.9.2014	19-23 (3)	0 - 32 IU/L
Serum ALT	10.11.2013-29.9.2014	14-25 (3)	0 - 31 IU/L
Serum alkaline phosphatase	10.11.2013-29.9.2014	77-96 (3)	35-104 IU/L
Serum Calcium	10.11.2013-29.9.2014	2.29-2.40 (4)	2.20 – 2.25 mmol/l
Serum Magnesium	23.4.2014	0.70 (1)	0.66-1.07 mmol/l
Serum TSH	10.11.2013	1.45 (1)	0.27-4.2 milli IU
Serum Insulin	4.2.2014 - 2.2.2015	9.8, 10.2, 12.8 (3)	2.6-24.9 milli IU/L
Serum C-peptide	4.2.2014	0.87 (1)	0.37-1.47 nmol/l
Serum ACTH (9 am)	20.5.2014	10.6 (1)	1.6-13.9 pmol/L
Serum Cortisol (9 am)	20.5.2014	273(1)	64-536 nmol/L
Serum FSH	10.11.2013-20.5.2014	51.9-55.2 (2)	1.7-21.5 IU/L
Serum LH	10.11.2013-20.5.2014	24.1-33.1 (2)	(NA) IU/L
Serum Estradiol	10.11.2013-20.5.2014	26, 46 (2)	(NA) pmol/L
Serum Progesterone	10.11.2013	<0.60 (1)	(NA) nmol/L
Serum Testosterone	10.11.2013	0.38 (1)	0.38-1.97 nmol/L
Serum Prolactin	10.11.2013-20.5.2014	105.7-198.9 (2)	102-496 milli IU

She was referred for conventional dietary adjustment. A trial of combination of Metformin and Saxagliptin previously on basis of wide fluctuation of blood glucose values with a predominance of early postprandial hyperglycemia followed by hypoglycemia was suggested 6 month previously. She has since stopped taking them due to gastrointestinal side effects.

The patient was so distressed with the symptoms that she requested bypass-reversal surgery. Symptoms have progressively worsened.

Other investigations confirmed post-menopausal status and excluded hypoadrenalism and renal and liver impairments. These results were tracked through the patient's electronic records. All the publically owned SEHA (Abu Dhabi Health Services Company) health facilities share all data recorded on all its sites. Other relevant investigations: Chest X-ray was normal and ultrasound scan of the abdomen was normal except for fatty liver (Table 1). It is noteworthy that she had had a single preoperative HbA1c reading was at 48 mmol/mol (6.5%) and this was corrected after surgery to levels between 41-44 mmol/mol.

After a week's long formal dietary modifications of small frequent meals and avoiding high glucose index foods with no benefit, she was started on increasing doses of Acarbose up to 100 mgs with each meal. A minimal improvement was observed in blood glucose was documented by SMBG (Figure 2).

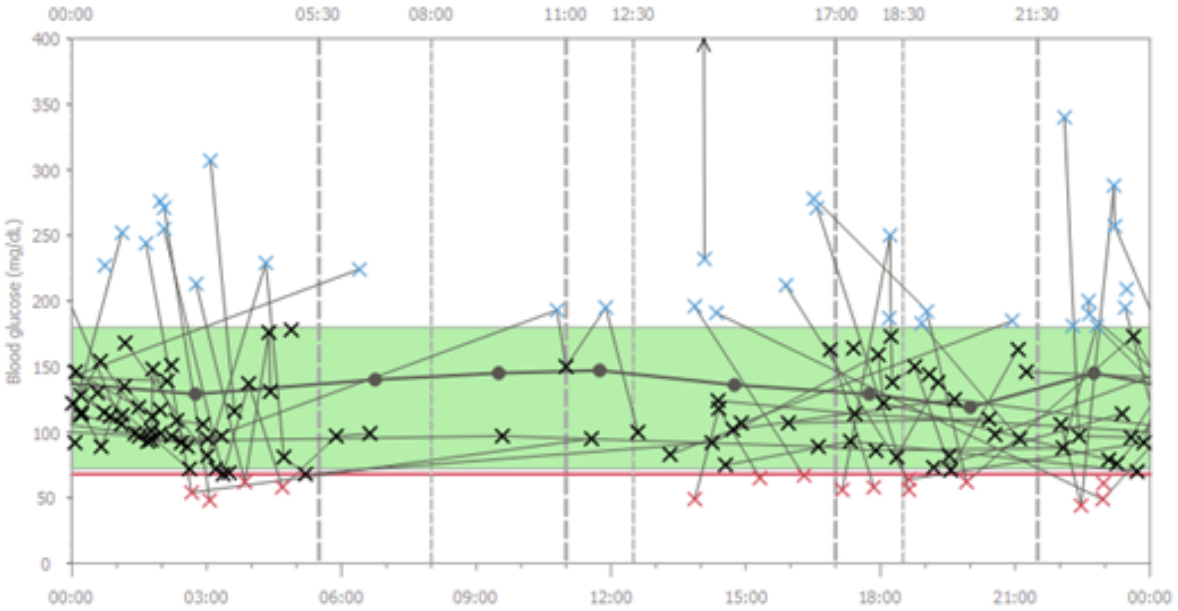

Figure 2. Self-monitoring of blood glucose demonstrating the wide fluctuating in blood glucose levels and persistent hypoglycemia while on Acarbose 100 mgs BID to TID in the two months prior to starting of Dapagliflozin (on 6th October 2015) thus demonstrating the inadequate control by Acarbose alone.

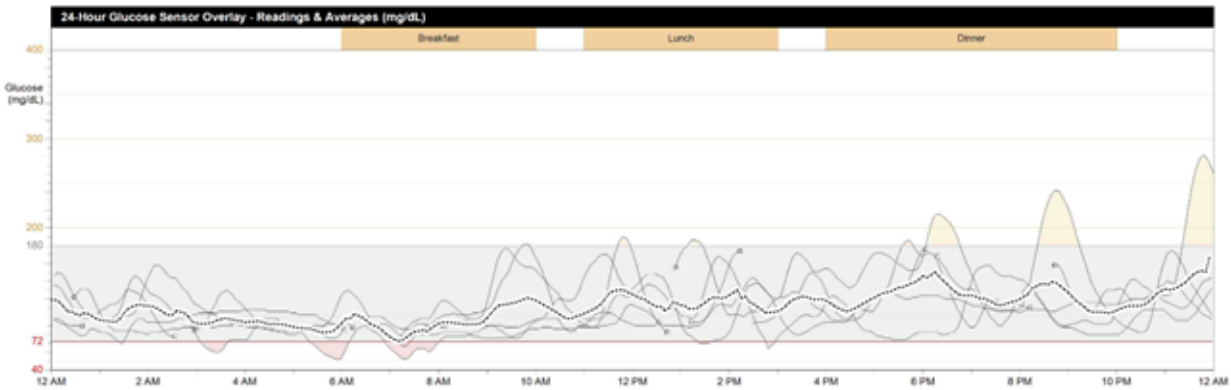

Figure 3. The continuous glucose monitoring (CGM) record demonstrating the reduction in hypoglycemia and less wide fluctuating after starting of Dapagliflozin 10 mgs after stopping Acarbose.

On basis of her obesity and the combination of high and low blood glucoses, a trial of an SGLT2 inhibitor (Dapagliflozin 10 mgs daily) in addition to acarbose was suggested (from 6th October 2015). Within 2 weeks, she experienced a remarkable symptomatic improvement and demonstrable reduction in both hyperglycemia and hypoglycemia. The patient progressively reduced the acarbose on her own volition to a complete cessation and remained well controlled on Dapagliflozin only as demonstated on CGM in March 2016 (Figure 3). The patient was satisfied with the response and agreed to continue on this management plan. Furthermore, the effect of the Dapagliflozin treatment documented by flash glucose monitoring (FGM) technology (6) using the FreeStyle® Libre™ (Abbott Diabetes Care, Alameda, CA) (7). The ambulatory glucose profile (APG) data captured both one week off and one week on treatment with dapagliflozin10 mgs confirmed the beneficial effect

of Dapagliflozin treatment on both hyper and hypoglycemia persisted even after complete withdrawal of Acarbose for a few months (Figure 4). Despite the improved HbA1c, the short lived postprandial hyperglycemia remains a cause for concern to the patient and ourselves. A short trial with Repaglinide was not helpful. Indeed, it worsened the hypoglycemia. As the main concern was hypoglycemia, it was agreed to continue the above treatment plan under close monitoring. The improvement has been sustained to the time of final revision of this report (last seen in clinic on 10th October 2016).

Discussion

Hyperinsulinemic hypoglycemia with neuroglycopenia is an increasingly recognized complication of RYGB due to the changes in gut hormonal milieu (1-5). The number of patients with postprandial hypoglycemia are likely to increase, as RYGB is the most popular bariatric procedure. Women who lost most of their excess weight after gastric bypass, long after the surgery was performed, and who did not have diabetes before surgery such as our patient are at the greatest risk.

The heterogeneity of the criteria used for diagnosis limits our knowledge of the size of the problem (8). Whipple's triad, with a glycemic threshold of 55 mg/dl as the diagnostic reference, has been favored by some workers (9). In practice, diagnosis is conventionally established by reproducing of hyperinsulinemic hypoglycemia during a mixed meal test rather than an oral glucose tolerance test (8). However, CGM may have the advantage of convenience in busy clinical practice (8). Well-validated hypoglycemia questionnaires may have a role for screening and surveillance purposes (8). In our patient, the classical mixed test was not employed and the initial physicians relied on the use of CGM illustrated in Figure 1. Therefore, under this case's circumstances, CGM was arguably an adequate alternative in a busy clinical practice. It revealed the episodes in the natural environment of the patient daily lifestyle and was also used to monitor the success of lifestyle modification and various pharmacological therapies.

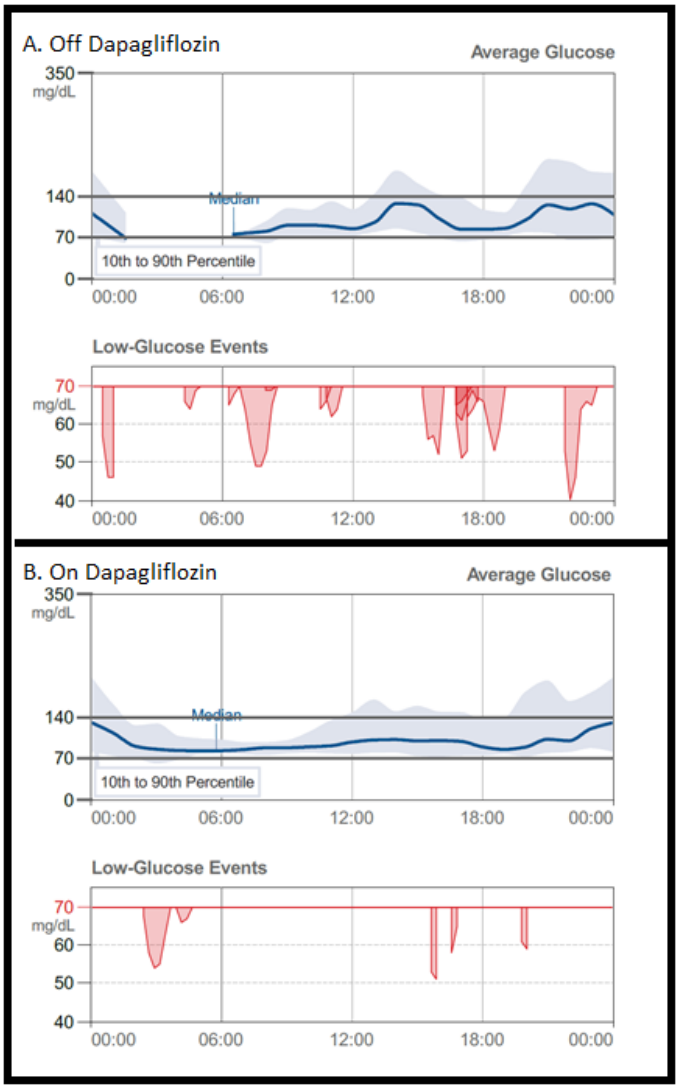

Figure 4. The AGP data captured for 8 days off (A) and 7 days on (B) treatment with Dapagliflozin 10 mgs demonstrating the effect of Dapagliflozin treatment on both hyper and hypoglycemia persisting months after withdrawal of Acarbose. The average blood glucose was lower (100 vs. 103 mg/dl); number of hypo events was lower (4 vs 12) and time spent in hypoglycemia was lower (58 vs. 89 minutes; 3 vs. 10%) on treatment versus off Dapagiflozin therapy.

The patient has already sought opinions from other clinics and she came to our clinic with a clear request of supporting a referral for reversal of the bypass so we had to act promptly. The patient was convinced that the hypoglycemia was related to the bariatric surgery and therefore she was not agreeable to any further investigative tests that were viewed from her point of

view as merely academic exercise. The patients fulfilled several criteria for increased risk of post bypass hypoglycemia. She was previously severely morbidly obese, middle aged, female, and she remarkable amount of weight and that her glucose intolerance status was just on the borderline based on a single HbA1c that later recovered.

Naturally, management included a systematic evaluation including history, biochemical analysis, and diagnostic testing to help the differential diagnosis. These were undertaken between the various clinics and all data were reviewed (Table 1). Our patient had no evidence of renal, hepatic or adrenal disease. Her premature menopause did not seem particularly relevant. Her hypoglycemic symptoms occurred only recently whereas she had had no periods from the age of 38 and she seems to have gone through the climacteric change smoothly. Hyperinsulinemic hypoglycemia was established in the previous institution on three occasions. We did not indulge in further evaluations of whether he had insulinoma on several counts; hypoglycemia occurred consistently in the postprandial phase, she was sustaining hyperglycemia during the early post prandial stage. Furthermore, she went through an "experiment of nature" of prolonged fasting tests during the previous month of Ramadan (daily fasting for 15-16 hours for 29 days) with no problems and during all this period she never sustained any episodes of fasting hypoglycemia (9). If anything, her serum insulin levels improved after the bariatric surgery (Table 1).

Management of post-bariatric hypoglycemia involves a range of maneuvers starting (10,11). Treatment usually begins with strict low carbohydrate diet which if not adequate is followed by medication therapy (12). The antidiabetic agent, Acarbose, being an alpha glucosidase inhibitor commonly used to slow down glucose absorption is commonly used for post-bariatric hypoglycemia. It is cheap and is readily available (13). Other treatments traditionally used for hypoglycemia. The Calcium channel blocker, verapamil, is a known traditional medication and was shown to be effective (14). Diazoxide is more commonly used for hyperinsulinemic hypoglycemia in childhood and also in adults. The long acting somatostatin analogue (Octreotide LAR) has also been recommended and its long-term efficacy in some cases has been demonstrated because of its inhibitory effect on insulin and GLP-1 secretion (15). Interestingly, GLP-1 analogues have successfully been used too (15). Their postulated mechanism of action is a stabilizing effect on blood glucose levels, although slowing of gastric emptying could be another plausible mechanism to explain their efficacy. There are also limited reports on successful use of Glucagon (16). It is noteworthy that some of these medications (e.g. Diazoxide) are not listed in regular hospital formularies. Others agents such as Octreotide LAR may be prohibitively expensive and the injection route of administration (Glucagon, Octreotide LAR and GLP-1 agonists) may not be particularly appealing to many patients. Gastric bypass reversal for the treatment of refractory hypoglycemia has been sparsely described. Physicians should try their best with medical therapies, if these fail, though surgery remains as the only possible option with permanent loss of substantial pancreatic reserve (17).

The patient was initially managed along the recommended lines of management (10,11). Treatment began with strict low carbohydrate diet which, followed by medication therapy (12). She was previously treated with Metformin and Saxagliptin justified by her treating physician elsewhere on basis of two counts 1) the history of diabetes and 2) the predominance of hyperglycemia mixed with hypoglycemia. This was very rational approach. However, the patient could not tolerate the medication nor she experienced any effect on hypoglycemia that was the main concern for her. She discontinued it completely before coming to our clinic. Acarbose was chosen as it is an agent with which we do have experience for management of diabetes, cheap and is readily available. Acarbose dose was gradually increased to its commonly used maximal dose of 100 mgs with meals (13).

Dapagliflozin is one member of a new class of oral antidiabetic agents that specifically inhibit sodium-glucose co-transporter (SGLT) 2 function in the kidney,

thus reducing renal glucose reabsorption and increasing glycosuria in diabetic individuals while reducing hyperglycemia (18). The use of SGLT2 inhibitors therapy primarily for postprandial hypoglycemia has not been described before. In this case, we were encouraged by his previous pre-operative history of borderline glycemic disorder (single HbA1c of 6.5%) and current coexistence of early postprandial hyperglycemia followed hypoglycemia. Though our target was reduction of hypoglycemia, we felt that use of Dapagliflozin is adequately covered within the licensed indications of Dapagliflozin by the co-existence of hyperglycemia and the preoperative HbA1c level (although technically 2 measurements are indeed required to establish the diagnosis of diabetes). We were pleasantly surprised to see the symptomatic improvement and marked reduction in both hypoglycemia and hyperglycemia. Due to the novel albeit plausible approach, we were reassured further on the validity of our management approach by demonstrating the effects of Dapagliflozin treatment persisting even after complete withdrawal of Acarbose (Figure 4). A simplistic interpretation of the observed benefit may focus on the assumption that with reducing the early postprandial hyperglycemia documented in this case on both CGM and her glucose meters (Figures 1 and 2), we could reduce the risk of hypoglycemia later. However, Dapagliflozin could have produced this effect by other mechanisms. Boner et al demonstrated that Dapagliflozin increase plasma glucagon in T2DM and it promotes glucagon secretion and hepatic gluconeogenesis in healthy subjects (19). Detailed discussion of the possible mechanisms is beyond the scope of this case report nor the expertise of the author. Further formal assessments are warranted to evaluate them formally under controlled circumstances that may help elucidate their mechanism of action.

In conclusion, the reported case has two novel aspects to it. Firstly, it is the first report of beneficial use of SGLT2 inhibition therapy for post-bariatric hypoglycemia. Use of SGLT2 inhibitors may be new option for management of post-bariatric hypoglycemia. SGLT2 inhibitors may be particularly useful in patients with combined hyperglycemia and hypoglycemia. Their use is plausible and is relevant as they are likely to help continued weight loss. Though it is the author's view that combination with Acarbose if tolerated would be more appropriate strategy. Indeed, this has been communicated to the patient during the latest consultation. Secondly, FGM was used here to evaluate post-bariatric hypoglycemia and its management for the first time. Use of FGM can be considered for assessments of ambulatory patients who respond positively to hypoglycemia screening questionnaires needs further evaluation. They have the advantage of convenience, low cost and longer period of continuous monitoring.

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Authorship

The author is solely responsible for the medical care of the patient and conception and preparation of this case report.

Compliance with ethical principles

1. Funding: None
2. Conflict of interest: None
3. Ethical Approval: The off label use of Dapagliflozin (rationale, benefits risks and alternatives) was explained to the patient by the treating physician (SAB) and witnessed by the diabetes educator (MK) and the patients consented to it. Full support was provided to the patient by phone contact to the treating physician and educator and open access to clinic. No Institutional Review Board approval is required for single case reports. Patient consented for use of her data anonymously for this report.

Special disclaimer

SMBG and CGM were conducted through the normal course of clinical care. Flash glucose monitoring technology was employed using supplies made available to SKMC purchasing department as a "pre purchasing evaluation", which is a standard business practice at SKMC. The manufacturers of all these technologies had no involvement whatsoever in any aspect of this case management. The manufacturer of Dapagliflozin has no prior knowledge of or any involvement in this case report.

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