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Euglycemic Diabetic Ketoacidosis Following Pancreaticoduodenectomy – Lessons for Surgeons and Other Clinicians

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Abstract

Euglycemic diabetic ketoacidosis (euDKA) is an emergency situation associated with diabetes which has recently drawn clinicians' attention due to its association with the administration of the novel class of antidiabetic's sodium-glucose cotransporter 2 (SGLT-2) inhibitors. The use of SGLT-2 inhibitors is on the rise, thanks to their primary and secondary cardioprotective effects. In the context of SGLT-2 inhibitor administration, major operation may precipitate euDKA. One such example is pancreatoduodenectomy, which is notorious for a multitude of associated complications, nevertheless has gained popularity over recent years because of its therapeutic impact on periampullary and pancreatic head malignancies. Familiarization with the technique has expanded its implication to patient groups who would otherwise be considered as "high risk". The surgeon and any related clinician must be aware of the rising complication of euDKA following pancreatoduodenectomy.

Keywords: Euglycemic diabetic ketoacidosis; Antidiabetic's; Sodium-glucose cotransporter 2; periampullary

Abbreviations: euDKA: Euglycemic Diabetic Ketoacidosis; SGLT-2: Sodium-Glucose Cotransporter 2; POD: Postoperative Day; BE: Base Excess; AG: Anion Gap; ICU: Intensive Care Unit; PD: Pancreatoduodenectomy; DGE: Delayed Gastric Emptying; DM: Diabetes Mellitus; PDAC: Pancreatic Adenocarcinoma; PP: Pancreatic Polypeptide; IPRDM: Immediate Post-Resection Diabetes Mellitus; DPP-4: Dipeptidyl Peptidase-4.

Clinical Vignette

A 65-year-old male, with a past medical history significant for acute coronary syndrome treated with angioplasty and stenting six months earlier and type 2 diabetes mellitus on oral antidiabetics, undergoes pancreatoduodenectomy for a 2 centimeter periampullary neuroendocrine tumor, combined with simultaneous radiofrequency ablation and wedge resection of oligometastatic hepatic disease. Nasogastric catheter is removed on postoperative day (POD) 2 and oral intake is progressively re-established from POD 3 onwards. Satisfactory glycemic control is achieved by means of insulin sliding scale. Immediate postoperative period is otherwise non-remarkable, except for polyuria of roughly 5 liters daily and two self-resolved episodes of flushing without

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hemodynamic compromise. On POD 5 the patient complains of epigastric fullness. Electrocardiogram, cardiac enzyme panels and triplex ultrasonography are non-remarkable for new-onset acute coronary syndrome, whereas reinsertion of nasogastric catheter drains less than ½ liter of gastric fluid. The abdomen is nontender, peritoneal drains have low output and bedside ultrasonography is negative for intra-abdominal free fluid or encapsulated fluid collections, whereas mesenteric vessels are patent, with normal pulse waves.

The patient suddenly becomes tachypneic (Kussmaul breath), lethargic and develops livedo reticularis and clammy, moist skin. Arterial blood gas analysis reads as follows: pH 7.037; pCO_2 6.8 mmHg; HCO_3^- 5.2 mmol/L; pO_2 133 mmHg; lactate 1.6 mmol/L; base excess (BE) -27.8 mmol/L; anion gap (AG) 18.8 mml/L; glucose 225 mg/dL; hemoglobin 10.2 g/dL. In view of imminent respiratory fatigue and arrest, we initiate aggressive resuscitation and transfer the patient to the intensive care unit (ICU), where he is intubated and continuously monitored. Therapeutic manipulations focus on avid rehydration, exogenous insulin administration and intravenous supplementation with sodium bicarbonate. After four hours of resuscitation, four flacons of sodium bicarbonate and numerous ABG checks, the ABG reads: pH 7.393; HCO_3^- 22 mmol/L, BE -3.1 mmol/L. Weaning from mechanical ventilation takes place next afternoon and the patient is discharged to the ward the next morning. Review of patient's drug history revealed administration of empagliflozin, a newer antidiabetic of the sodium glucose cotransporter-2 (SGLT-2) inhibitor class, which had been discontinued the previous day of the operation.

Interrelations Among Pancreatic Neoplasia, Pancreatic Surgery and Diabetes Mellitus

Pancreatoduodenectomy (PD), or Whipple's procedure with its variants, has increasingly gained popularity lately for the management of pancreatic and periampullary neoplasms, as its safety has increased, thanks to careful patient selection, meticulous surgical technique and the development of enhanced protocols of perioperative care [1,2]. Familiarization with pancreatoduodenectomy has inspired confidence in performing this operation and offering it as a promising therapeutic option in patients with multiple comorbidities, as the one described in the above-mentioned clinical vignette. Nevertheless, PD has serious complications that should always be kept in mind, and these comprise but are not limited to the "popular" ones, i.e. post-pancreatectomy hemorrhage (PPH) [3], post-operative pancreatic fistula (POPF) [4,5], and delayed gastric emptying (DGE) [6]. Indeed, clinical experience has taught that preoperative comorbidities not only increase the risk for PPH, POPF and DGE, but also predispose to incidents relevant to the underlying pathology, thus increasing in-hospital morbidity and mortality [7-9]. Most importantly, those incidents cannot be reliably predicted with current preoperative assessment modalities [10].

Diabetes mellitus (DM) is one such pathology, intimately associated both with pancreatic carcinogenesis and pancreatic surgery. The reciprocal relationship between DM and pancreatic adenocarcinoma (PDAC) has long been established [11,12]: hyperinsulinemia and insulin resistance play a pivotal role in the development and aggressiveness of PDAC [12-14]; conversely, PDAC is a diabetogenic condition, either per se or by sharing common risk factors with DM, such as obesity or inherited and epigenetic predisposition [15-17]. Post-pancreatectomy diabetes is a subcategory of type 3c or pancreatogenic diabetes, attributed to pancreatic polypeptide (PP) deficiency, which is more prominent when the head of the pancreas and the uncinate process are excised (as in the Whipple's procedure), because these anatomic areas are rich in PP-cells [18]. PP deficiency leads in turn to isolated hepatocellular insulin resistance with persistent unsuppressed glucose production and fasting hyperglycemia [11]. Of note, rarely do patients with post-pancreatectomy diabetes manifest DKA, as their hyperglycemia is relatively mild [11]. New-onset diabetes post-PD may affect as many as 20% of patients [19,20], whereas diabetic patients who undergo PD may experience disruption of their preoperatively well-controlled DM at a rate of 26% [20]. Another relentless issue that every pancreatic surgeon faces is immediate post-resection diabetes mellitus (iPRDM), which may affect up to 4% of patients undergoing PD after excluding secondary causes of glycemic dysregulation (i.e. POPF or sepsis) and is associated with the status of preoperative glycemic control and the amount of the excised pancreatic tissue [21].

Euglycemic Diabetic Ketoacidosis in the Context of Pancreatic Surgery

Diabetic emergencies are not infrequent following PD. Postoperative hypoglycemia is characteristic of total pancreatectomy [22,23], however it may occur in the setting of early dumping and DGE following pancreaticoduodenectomy as well [24], or may be iatrogenic as a consequence to high sensitivity to exogenous insulin administration [11], a common practice in the perioperative period. A complication that has recently emerged following major surgery in diabetic patients is euglycemic diabetic ketoacidosis (euDKA), especially in those on the newer class of sodium glucose cotransporter-2 (SGLT-2) inhibitors, but also in those on dipeptidyl peptidase-4 (DPP-4) inhibitors [25]. These classes of antidiabetics are prescribed with increasing frequency nowadays, owing to their cardioprotective role, which increases their relative advantage for primary and secondary prevention of coronary events in diabetic patients. Accumulating evidence suggests that major surgery is a

potent trigger of euDKA in patients taking SGLT-2 inhibitors [26-28]. Additionally, numerous recent case reports and series underline the manifestation of euDKA following bariatric [29,30], as well as non-bariatric major surgery [31,32]. Regarding specifically pancreatic surgery, there has been a recent report of two patients who had undergone pancreatoduodenectomy and distal pancreatectomy, respectively, and manifested euDKA that was attributed to the concomitant use of SGLT-2 inhibitors in the perioperative period.[32] Interestingly, SGLT-2 inhibitors may induce euDKA even after cese of administration unless they are discontinued more than 48 hours preoperatively, i.e. more than 3 half-lives (T½≈12 hours) [33].

Diabetic ketoacidosis is by definition a state of hyperglycemia and acidemia, manifested as: polyuria, polydipsia, weakness, nausea and vomiting, altered sensorium, abdominal cramps or pain, contraction of extracellular fluid volume, Kussmaul respiration and acetone-odoured breath; and precipitated by serious systemic insults, such as infection, myocardial infarction, trauma, undiagnosed DM and non-compliance with antidiabetic regimens etc [34]. Typically, arterial pH is ≤7.3, serum bicarbonate ≤1.5 mEq/L and anion gap >12 mmol/L, whereas the threshold for hyperglycemia is somewhat in literature, ranging from 200 mg/dL to 250 mg/dL according to the Joint British Diabetic Society and American Diabetes Association, respectively [35]. Nevertheless, glucose level is not taken into consideration when grading the severity of DKA. Additionally, DKA is a rather rare phenomenon in individuals suffering from T2DM (0.32-2 per patient-years) [36], owing in part to patient and physician alertness and mostly due to the effectiveness of modern therapies. The rarity of this condition is the reason why specialists from non-familiar fields (such as general surgeons) may not recognize this condition promptly, even in its typical form. Consequently, alertness should be raised over the most "modern" variant of DKA, that is euglycemic DKA (euDKA), a condition first described in a seminal report by Munro and colleagues back in 1973, which is manifested within a glycemic milieu that one would not normally expect DKA to develop (i.e. blood sugar ≤300 mg/dL) [37]. The patient described in the previous clinical scenario perfectly fits in this state of euDKA.

SGLT-2 inhibitors may precipitate either euglycemic or typical DKA, the determinant being the balance between hepatic glucose production and glycosuria [38]. Despite the challenge of initial recognition of euDKA, *post hoc* differentiation between euDKA and typical DKA is somewhat easier, given that the former is heralded by very low pH and bicarbonate levels [28], as in the presented case. The mechanism through which SGLT-2 inhibitors precipitate euDKA is as follows: SGLT-2 inhibitors acting on the kidney induce glycosuria and lower sodium reabsorption [32-38]. Glycosuria affects plasma glucose levels and the ensuing hypoglycemia leads to glucagon release by the pancreas and lipolysis by the liver (induction of HMG-CoA synthase by glucagon – Pathway 1) and adipose tissue (induction of hormone-sensitive lipase by glucagon – Pathway 2)[39]. Low sodium reabsorption in the proximal tubule leads to high levels of ketone bodies, probably because of overproduction rather than reduced renal clearance (Pathway 3) [39,40]. The net effect of all three pathways is increased ketogenesis by the liver.

The manifestation of euDKA following pancreatic surgery, as in the case vignette previously, is multimodal and multifactorial and SGLT-2 inhibitors should not be considered the sole culprits lightheartedly. Perry *et al.* recently showed in an experimental model that dehydration and insulinopenia are necessary and sufficient conditions for the development of euDKA in subjects treated with SGLT-2 inhibitors [41]. A patient who has undergone pancreatoduodenectomy (i.e. a major procedure and a diabetogenic one due to loss of PP-cell mass) and their postoperative course has been complicated by occult delayed gastric emptying (i.e. a state of dehydration and low-carbohydrate intake) [38], exactly like the one outlined in the index case, fulfills the requirements to develop euDKA and previous administration of SGLT-2 formulates the appropriate biochemical milieu for the perfect storm to take place.

Emergence of "Novel" Complications in the Era of Personalized Medicine – Lessons for the Surgeon

Pancreatoduodenectomy is notorious among surgeons for being associated with a constellation of potential complications owing both to the technical difficulties that stem from the anatomic location and the properties of the tumor, as well as to the great impact it has as a procedure on the physiology of the patient. Familiarization with the technique has expanded the application of PD to patients who would be deemed inappropriate surgical candidates in the past due to multiple comorbidities. Amidst this ambiguous context, side effects of modern medications may serve as additional sources of postoperative morbidity. However up-to-date a clinician may be, it is almost impossible to manage this multitude of evidence emerging constantly and on a daily basis. A multidisciplinary team approach, with the involvement of experts on different fields (i.e. Diabetologists, Dieticians, Clinical Pharmacologists, Intensive Care Specialists etc) is currently the only efficient weapon against the above-mentioned adversities, but it may be impractical given the high workload and the plentiful of patients that Surgeons are called to manage in their daily practice. Future

perspectives should focus on platforms for managing the "big data" and offering real-time assistance to surgical decision making, as the ones implemented by machine learning and artificial intelligence [41-43].

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