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Pancreatic surgery and tertiary pancreatitis services warrant provision for support from a specialist diabetes team

Mavroeidis VK et al. Specialist diabetes team support for pancreatic services

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Abstract

Pancreatic surgery units undertake several complex operations, albeit with considerable morbidity and mortality, as is the case for the management of complicated acute pancreatitis or chronic pancreatitis. The centralisation of pancreatic surgery services, with the development of designated large-volume centres, has contributed to significantly improved outcomes. In this editorial, we discuss the complex associations between diabetes mellitus (DM) and pancreatic/periampullary disease in the context of pancreatic surgery and overall management of complex

pancreatitis, highlighting the consequential needs and the indispensable role of specialist diabetes teams in support of tertiary pancreatic services. Type 3c pancreatogenic diabetes mellitus (T3cDM), refers to DM developing in the setting of exocrine pancreatic disease, and its identification and management can be challenging, while the glycaemic control of such patients may affect their course of treatment and outcome. Adequate preoperative diabetes assessment is warranted to aid identification of patients who are likely to need commencement or escalation of glucose lowering therapy in the postoperative period. The incidence of new onset diabetes after pancreatic resection is widely variable in the literature, and depends on the type and extent of pancreatic resection, as is the case with pancreatic parenchymal loss in the context of severe pancreatitis. Early involvement of a specialist diabetes team is essential to ensure a holistic management. In the current era, large volume pancreatic surgery services commonly abide by the principles of enhanced recovery after surgery (ERAS), with inclusion of provisions for optimisation of the perioperative glycaemic control, to improve outcomes. While various guidelines are available to aid perioperative management of DM, auditing and quality improvement platforms have highlighted deficiencies in the perioperative management of diabetic patients and areas of required improvement. The need for perioperative support of diabetic patients by specialist diabetes teams is uniformly underlined, a fact that becomes clearly more prominent at all different stages in the setting of pancreatic surgery and the management of complex pancreatitis. Therefore, pancreatic surgery and tertiary pancreatitis services must be designed with a provision for support from specialist diabetes teams. With the ongoing accumulation of evidence, it would be

reasonable to consider the design of specific guidelines for the glycaemic management of these patients.

Key words: Pancreatectomy; Pancreatoduodenectomy; Whipple's; Pancreatitis; Diabetes specialist; Type 3c pancreatogenic diabetes mellitus

Core tip: In this editorial, we discuss the complex associations between diabetes mellitus and pancreatic/periampullary disease in the context of pancreatic surgery and overall management of complex pancreatitis, highlighting the consequential needs and the indispensable role of specialist diabetes teams in support of tertiary pancreatic services. In these settings, there is accumulating evidence that adequate glycaemic control at all stages improves outcomes, and that early involvement of specialist diabetes teams is of paramount importance to ensure a holistic management approach. The design of specific guidelines for the glycaemic management in these settings is warranted.

INTRODUCTION

Pancreatic surgery units deliver a range of operations for benign, pre-malignant and malignant pancreatic and periampullary diseases[1]. These are notoriously complex operations, including the classic Whipple's pancreatoduodenectomy (PD) and its pylorus-preserving variation; distal pancreatectomy (DP) and its extended form called left pancreatectomy, with or without splenectomy; the more radical version of the latter, i.e. radical antegrade modular pancreatosplenectomy (RAMPS); central

pancreatectomy; total pancreatectomy (TP) with or without splenectomy; tumour enucleations and other less common procedures[1, 2]. In addition, operations undertaken for complications of acute pancreatitis or for chronic pancreatitis may involve various degrees of resections of pancreatic parenchyma and a number of different reconstruction techniques. Furthermore, pancreatitis itself may result in variable reduction of the functional pancreatic parenchyma. The aforementioned operations are associated with significant morbidity and mortality[1]. In recent decades, the centralisation of pancreatic surgery services with development of designated large-volume centres has gradually improved outcomes in conjunction with improvements in patient selection and operative techniques[1]. Characteristically, for the complex Whipple's operation, the perioperative mortality has fallen to less than 4.0% in high-volume centres, while postoperative morbidity remains high, up to 60%[1, 3, 4].

DIABETES MELLITUS AND PANCREATIC DISEASE

Diabetes mellitus (DM) may be associated with pancreatic and periampullary surgical diseases in different forms, particularly new-onset diabetes (NOD) as a potential presenting symptom of pancreatic ductal adenocarcinoma (PDAC)[5]. The most prevalent theory for the pathogenesis of the latter is that of a paraneoplastic manifestation induced by diabetogenic factors[6]. Type 3c pancreatogenic diabetes mellitus (T3cDM), refers to DM developing in the setting of exocrine pancreatic disease, including PDAC, chronic pancreatitis (CP), haemochromatosis, cystic fibrosis, and previous pancreatic surgery[7, 8]. The entity remains underdiagnosed and

underreported while its profile is characterised by low to normal fasting C-peptide, negative islet antibodies, coexistence with pancreatic exocrine insufficiency and often challenging glucose control with hyper- and hypoglycaemia, whilst episodes of ketoacidosis are rare. Whilst some individuals may be at least initially managed with oral agents, many will need insulin treatment[7-9]. T3cDM developing as a result of acute or CP is a heterogeneous entity with variable clinical presentations, frequently misdiagnosed and treated as type 2 DM[10-12]. Meta-analyses from 2014 and 2019 found a rate of development of NOD ranging from 15% at 12 months following admission with acute pancreatitis, with a subsequent increase to 23% in following years[13-15]. Recent studies have shown an approximate 10% rate at 12 months[16, 17]. Furthermore, many patients who require treatment for pancreatic or periampullary disease may have pre-existing DM[5]. In recent multicentre studies, approximately 20% of patients who underwent PD for malignancy had a preoperative diagnosis of DM[3, 4]. Remarkably, up to 85% of patients with PDAC have hyperglycaemia or diabetes, while patients with NOD have a 5-8-fold higher risk of PDAC diagnosis within 1-3 years of developing DM[18]. Notably, recognition of NOD as a presenting symptom of PDAC is crucial for its early diagnosis, and distinguishing this form from type 2 DM has attracted significant interest in the last decade[6, 7, 18, 19].

DIABETES MELLITUS IN THE PANCREATIC SURGERY/PANCREATITIS SETTING

The group of patients with pancreatic/periampullary surgical disease and pre-existing prediabetes or DM requires special attention, as their glycaemic control may affect their course of treatment and outcome[20, 21]. Furthermore, their diabetes management may be complex postoperatively and require intensification of treatment[18, 19]. Notably, Tariq et al.'s study of 216 patients undergoing DP, detected 40% of patients being preoperatively unaware of their dysglycaemic status (prediabetes or DM). Importantly, those with prediabetes were at increased risk of postoperative diabetes. Therefore, the authors concluded that adequate preoperative diabetes assessment is warranted for all patients ahead of pancreatic resection, to help identify those most likely to need initiation or escalation of glucose lowering therapy in the postoperative phase[22]. A higher rate of acute kidney injury[20] and postoperative pancreatic fistula (POPF) has been reported by some studies in diabetic patients undergoing pancreatic resection[20, 21], while other studies have suggested absence of relationship[4] or even a possible protective effect of DM against POPF, owing to lower rates of high-risk pancreatic gland features[23, 24]. Furthermore, as already mentioned, as a result of removal/loss of pancreatic parenchyma, new onset T3cDM may develop in the postoperative, as well as in the post-pancreatitis setting. It has been hypothesised that DP may confer a higher risk of postoperative development of diabetes compared to PD, as 70% of the β-cell mass appears to be located in the body and tail[22, 25]. Tariq et al., in their study of 216 patients undergoing DP, found that 36% of non-diabetic and 57% of prediabetic patients developed DM at 2-year follow-up postoperatively[22]. Overall, the incidence of development of diabetes after

pancreatic resection is widely variable in the literature, owing to different operative techniques, heterogeneous groups and the retrospective nature of most studies[22].

CP is a complex disease not infrequently requiring surgical treatment. The consensus statement of the International Study Group for Pancreatic Surgery (ISGPS) on the standards for reporting on surgery for CP include the presence/absence of DM in the domain of "clinical baseline prior to surgery", and postoperative DM in the domain of "minimum outcome dataset"[26], using the terminology and reference ranges of the World Health Organization[27].

Another important group is represented by patients scheduled for TP with or without splenectomy, who will certainly have insulin-requiring diabetes postoperatively, regardless of their preoperative state[28]. These patients require specialist care prior to their surgery wherever possible to ensure adequate education for the required insulin treatment and glucose monitoring. Early involvement of the specialist diabetes team is essential to ensure holistic management[9]. Specifically in the management of CP, the role of total pancreatectomy with islet autotransplantation (TPIAT) has been explored to avoid unstable postoperative diabetes. Consensus statements were based on strong agreement that, among other benefits, TPIAT offers glycaemic benefit over TP alone, and that other disease features as well as the islet mass transplanted may impact the outcomes[28].

As mentioned, a number of pancreatic diseases, including pancreatic tumours, CP and episodes of acute pancreatitis (especially necrotising[14]), may reduce the functional parenchyma of the gland and ultimately result in DM, either directly or by requiring surgical removal of part of the pancreas by the aforementioned different forms of

pancreatectomy. The impact of these operations on the endocrine function of the pancreas depends on the extent, but also on the prior state of glycaemic control[9, 29]. Importantly, it also needs to be noted that up to 35% of patients with pre-existing DM are reported to record improved glycaemic control after pancreatectomy[30, 31].

ENHANCED RECOVERY AFTER SURGERY CONCEPT AND PERIOPERATIVE GLYCAEMIC CONTROL

In the current era of centralisation of services, which in the case of pancreatic surgery has evidently led to improved morbidity, mortality and oncological outcomes[1], large volume pancreatic surgery services worldwide commonly follow the principles of an enhanced recovery after surgery (ERAS) concept[32-34]. This is reflected in dedicated protocols, most of the time designed and approved locally, but largely following generally accepted principles in the field of pancreatic surgery. Despite possible variations, it is expected that pancreatic ERAS pathways include provisions for optimisation of the perioperative glycaemic control[32-34]. The most recent ERAS recommendations for PD from 2019, based on the best available evidence and on expert consensus, include postoperative glycaemic control among the standard parameters of the pathways[32]. They highlight that the available evidence supports an association between elevated blood glucose and adverse clinical outcomes, both in diabetic and non-diabetic patients. The optimal perioperative glycaemic target remains unclear, but in general, glucose levels should be kept as close to normal range as possible without causing hypoglycaemia. The level of evidence for the aforementioned recommendations is moderate, while the grade of recommendation

is strong[32]. In forming these recommendations, a number of important facts have been taken into account. It has been noted that early hyperglycaemia (>7.8 mmol/L), high glucose variability and high glucose values in the early period after PD, are significantly associated with development of complications[35, 36]. A high preoperative HbA1c level has been associated with almost a threefold increased risk of complications after surgery compared to normal levels[37]. A randomized controlled trial of patients undergoing liver and pancreatic surgery, including PD, whilst on intensive care, compared a group receiving perioperative intensive insulin therapy with a target blood glucose range of 4.4–6.1 mmol/L to an intermediate insulin therapy group with a blood glucose range of 7.7–10.0 mmol/L. The intensive therapy group recorded lower rates of surgical site infection, POPF and shorter length of stay[38]. However, other multicenter trials in the intensive care setting, but not limited to post pancreatic surgery, have demonstrated that intensive insulin treatment results in increased incidence of hypoglycaemia and mortality compared to moderate glucose control[39-41]. The optimal levels of early postoperative blood glucose associated with improved clinical outcomes remain unclear[42], and notably no studies have examined glucose targets outside of the intensive care setting, where the challenges of maintaining tight glucose control are even higher.

A web-based survey undertaken through the ERAS® society and the International Hepato-Pancreato-Biliary Association membership was recently published and aimed to explore global awareness, perceptions and practice of ERAS for PD. Among 140 respondent surgeons, the majority rated highly the importance of postoperative glycaemic control (90%) as a component of the protocols[43]. Importantly, surgeons

performing <20 PDs per year were likely to face more significant challenges in implementing postoperative glycaemic control locally in the context of their enhanced recovery practice ($p = 0.001$)[43]. The guidelines of the Joint British Diabetes Societies (JBDS) for Inpatient Care Group from 2016 recommend that, for diabetic patients undergoing surgery, the principles of ERAS programmes should be followed[44].

GUIDANCE, PERFORMANCE INDICATORS AND MEASURED PRACTICE

As mentioned, the level of perioperative glycaemic control may have a direct impact on the course of recovery, length of stay and surgical outcomes. Ideally, to benchmark the quality of perioperative glycaemic control, appropriate available guidance and definitions can be used. In the United Kingdom (UK), various guidelines are available that can be useful in aiding perioperative management of DM, such as those issued by JBDS, the Association of Surgeons of Great Britain and Ireland (ASGBI) and the Association of Anaesthetists of Great Britain and Ireland (AAGBI)[44-46]. The Healthcare Quality and Improvement Partnership (HQIP) commissioned the National Diabetes Inpatient Audit (NaDIA) which first took place in 2010 and followed an annual pattern. The NaDIA is based on information gathered by hospital staff about the quality of diabetes care provided to inpatients with DM during their hospital stay. For its purposes, a 'good diabetes day' was defined as any day in the management of a patient with DM when the number of tests per day followed the guidelines, there was no more than one blood glucose measurement of >11mmol/L and no measurement of <4mmol/L. The 2016 report, based on information collected from 209 acute hospitals in England and Wales, underlined that 28% of hospitals had no

diabetes inpatient specialist nurses[47]. The ThinkGlucose campaign led by the National Health System (NHS) Institute for Innovation and Improvement expects close cooperation between the specialist diabetes team and hospital staff, for all hospitalised diabetic patients [48]. The NaDIA 2016 report found that 31% of people with DM who needed review by the diabetes team based on the ThinkGlucose criteria, did not meet this expectation[47], although notably this audit looked at all in-patients, not specifically those post pancreatic surgery. The National Institute for Health and Care Excellence (NICE) Quality Standard in England highlights that people with DM need access to a specialist diabetes team[47]. The NaDIA 2016 report underlined that hospitals should ensure that there are enough staff on the diabetes team to provide support in the delivery of safe diabetes care[47].

In 2018, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) published a report with wide multidisciplinary input, entitled "*Highs and lows*", after reviewing the quality of perioperative care provided to diabetic patients >16 years old undergoing a surgical procedure in the UK (not confined to pancreatic surgery)[49]. This included assessment of patient care and service structure, at clinical and organisational level, respectively. Importantly, perioperative diabetes management was examined and several deficiencies were highlighted. A lack of clinical continuity across the different specialties in the perioperative pathway was noted and the absence of joint ownership and a joint multidisciplinary approach implied that DM management was falling between gaps in the surgical pathway[49], especially given that diabetes can be managed in primary care, community services or hospital-based specialist teams. Note was made of key diabetes team members being

under-involved in patient management, including specialist diabetes nurses, pharmacists and dietitians[49]. Regular monitoring of blood glucose was underutilised at all phases of perioperative care[49]. The report emphasised that in 35.8% of diabetic patients in the study there was room for improvement in the clinical care, while 14.1% of cases required improvement in both clinical and organisational systems of care[49]. A number of areas for improvements and relevant recommendations were made[49]. Among those recommendations, the primary focus for action included the appointment of a Clinical Lead for Perioperative Diabetes Management. Among other tasks, they should lead at a local level on the writing and implementation of a policy for the multidisciplinary management of patients with DM who require surgery, in agreement with the guidelines of the JBDS[44, 49]. Importantly, only 28% of hospitals were noted to have a named clinical lead for perioperative diabetes management. To ensure adequate assessment and optimisation of diabetes in view of upcoming elective surgery, the Clinical Lead would also be responsible for the appropriate utilisation of a standardised referral process, as well as for ensuring that diabetic patients undergoing surgery are safely handed over for close monitoring and adequate glycaemic control. The report also highlighted that for most of the patients whose diabetes was not managed by all the appropriate staff, early involvement of specialist diabetes nurses would have been valuable[49]. Additional recommendations included the development of a preoperative assessment clinic policy, as 43.4% of such clinics did not have a specific relevant policy, while where this existed, wider multidisciplinary involvement was variable. It was also recommended that the Clinical Lead ensures that diabetic patients attending a

preoperative assessment clinic have access to input from a specialist diabetes nurse and other members of the diabetes team, as required, and receive written guidance about the preoperative management of their DM. Moreover, it was recommended to avoid cancellations of elective surgical procedures in patients with DM, especially for known clinical issues, to locally audit such cancellations and to take appropriate action accordingly[49]. Diabetic patients should be prioritised on the operating lists to avoid prolonged starvation; 19.4% of patients appeared to have not been scheduled appropriately. Importantly, patients with diabetes should be provided with education and comprehensive information about their diabetes management at discharge from hospital as part of the discharge planning process, with the involvement of diabetes specialist nurses and the Clinical Lead for perioperative diabetes management. In 20% of patients, adequate discharge arrangements for diabetes care were lacking[49]. Furthermore, largely in response to the findings of the NaDIA and the NCEPOD report, the Centre of Perioperative Care (CPOC) published in 2021 the "*Guideline for perioperative care for people with diabetes mellitus undergoing elective and emergency surgery*", consisting of a national joint standard and policy[50]. Understandably, whilst not all of these recommendations will be relevant to pancreatic surgery for malignancy, where it will rarely be appropriate to delay surgery to optimise metabolic control, they are important when elective surgery is planned for non-malignant pancreatic conditions. The CPOC guideline involved relevant recommendations across the wide spectrum of the perioperative pathway of diabetic patients undergoing elective and emergency surgery, including the referral, the stage before surgery, individualised plans and communication with healthcare teams, the time of

admission, intraoperative management, ward management and time of discharge[50]. Notably, the recommended range of capillary blood glucose to maintain in the wards was set at 6-12 mmol/L[50].

Surgical and anaesthetic departments are expected to ensure morbidity and mortality (M&M) meetings for elective and emergency surgery, while the 2011 guidelines of the Royal College of Surgeons on emergency surgery recommend that regular departmental clinical audit and M&M meetings should be undertaken and reported to the clinical governance committee[51]. In the NCEPOD study, only 25% of hospitals reported that an audit was performed on perioperative diabetes management[49].

Even though the NaDIA and the NCEPOD reports were not specifically focused on evaluating pancreatic surgical services and the provision of emergency pancreatitis surgery, their findings are of particular value to these services, given their particular challenges in perioperative diabetes care. However, there are a number of features of pancreatic surgery that mean specific guidelines would be helpful. This includes the very high prevalence of preoperative diabetes, the frequent use of insulin in Type 3c diabetes[13-17], and the fact that for patients who require a long hospital stay facing complications of pancreatitis or pancreatic surgery, the level of glycaemic control may have a further impact on the course and duration of recovery by affecting the course and management of complications.

Notably, nutritional assessment is essential in the preparation of diabetic patients for surgery as the reintroduction of nutrition postoperatively may be delayed and the disease process itself may result in dietary alterations. Glycaemic control is not uncommonly challenging in the postoperative period[48]. This is particularly

applicable in patients undergoing pancreatic surgery. Furthermore, both patients undergoing pancreatic surgery and patients with severe pancreatitis may require short or long courses of Total Parenteral Nutrition. This may further complicate their glycaemic control which may become particularly challenging in this setting[52]. It is necessary that these groups of patients receive direct input from designated diabetes teams, with access to appropriate multi-disciplinary diabetes specialist clinicians, which may include specialist nurse or other practitioners, dieticians and diabetologists as required.

One aspect requiring special attention is the required education for patients undergoing pancreatic surgery or recovering from severe pancreatitis, who have or are likely to encounter changes of their initial glycaemic state, either in the form of new onset prediabetes/diabetes, or worsening of previous prediabetes/diabetes, and potentially a need for new forms of treatment.

There is clear agreement that patients undergoing pancreatic surgery should be evaluated by a diabetes team preoperatively and have sufficient insight into the management of their potential postoperative NOD[9]. Adequate follow-up with a diabetologist, a specialist diabetes nurse and a dietitian should be ensured in the outpatient setting, for appropriate education, optimisation of the glycaemic control and personalisation of insulin therapy[9]. The extent of pancreatic resection should be taken into account in planning the patient's diabetes education. For instance, in those undergoing a standard DP, the risk of development of DM is commonly uncertain, and needs to be assessed before, immediately after surgery, at discharge and

subsequently during follow-up visits, since the glycaemic control may worsen or improve postoperatively[9]. -People undergoing TP with or without splenectomy require intensive diabetes education, including dietary advice, and follow-up under a specialist diabetes team. Even though there is wide agreement on this matter, there is considerable disparity in the education patients receive preoperatively and postoperatively. Also, preoperative diabetes assessment is not practised uniformly[53]. Identifying preoperatively patients who are unwilling or incapable to monitor and maintain glycaemic control is crucial[9]. Notably, some authors advocate that inability to perform these tasks and lack of understanding on the part of the patient and/or family should be considered contraindications for TP[54]. Maker et al., noted significantly reduced postoperative morbidity and mortality following referral for preoperative patient education and subsequent surgical reassessment, to determine whether adequate understanding, support and resources were in place preoperatively[54]. Furthermore, improved outcomes are recorded in the presence of follow-up diabetes education with a specialist team comprising diabetologist, diabetes nurse and dietitian. It is plausible that close collaboration between the patient and the diabetes specialists is essential to ensure the best possible care after pancreatic surgery, given the increased risk of hypoglycaemia in conjunction with the plethora of further potential issues to consider, including injection technique, self-monitoring of blood glucose, ketones, exercise, driving guidelines, travel, and alcohol intake[9]. Moreover, readmission rates are considerable for these patients, hence, further indicative of the requirement for additional input in the outpatient setting[9]. Consequently, discharge planning is essential for the holistic care of diabetic patients. Given the significant

perioperative stress and dietary changes, these patients require close monitoring to ensure adequate glycaemic control in accordance with the recommended range of 6-12 mmol/L[49, 50]. Inadequate discharge planning can cause readmissions for complications related to poor glycaemic control[49]. It is advised that ward staff work in close partnership with the DM specialists to ensure appropriate discharge criteria are met, and a collaborative process is in place. Patient education is fundamental to this process, as is the diabetes team that will follow up the patient[49].

CONCLUSIONS

Adequate glycaemic management is an essential aspect of the optimal provision of pancreatic surgery services and tertiary pancreatitis services, under the concept of centralisation and strive to meet standards of excellent care. Hence, the value of supporting these services with specialist input from diabetes teams is indispensable, and may become apparent at various stages of the clinical management. For patients undergoing elective pancreatic resection, this process starts at the preoperative stage with appropriate referral, evaluation and input, including education. This continues during the period of admission with the goal of optimising glycaemic control and providing adequate education, followed by regular post-discharge follow-up as required in each case. Equally, peri-admission and post-discharge specialist diabetes input should be made available in the complex management of patients with severe episodes of pancreatitis, as required. Adequate glycaemic control at all stages can clearly impact outcomes and is therefore essential. As such, it is plausible to consider that pancreatic surgery services and tertiary pancreatitis services must be designed

with a provision for support from specialist diabetes teams and that close working between surgical and diabetes teams is essential. As evidence is accumulating, it would be reasonable to consider the design of specific guidelines for the glycaemic management of these patients.

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