Insulin therapy in organ donation and transplantation

Iestyn M. Shapey MSc\textsuperscript{1,2} | Angela Summers PhD\textsuperscript{1,2} | Petros Yiannoullou MBBS\textsuperscript{1,2} | Jonathan Bannard-Smith MBChB\textsuperscript{3} | Titus Augustine MS\textsuperscript{1,2} | Martin K. Rutter MD\textsuperscript{1,4} | David van Dellen MD\textsuperscript{1,2}

\textsuperscript{1}Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Medicine, Biology and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK
\textsuperscript{2}Department of Renal and Pancreatic Transplantation, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
\textsuperscript{3}Department of Critical Care, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK
\textsuperscript{4}Manchester Diabetes Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Correspondence
Iestyn M. Shapey, Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Medicine, Biology and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester M13 9PL, UK.
Email: iestyn.shapey@manchester.ac.uk

Funding information
Medical Research Council (UK); Royal College of Surgeons of Edinburgh.

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.13728.

Abstract:
Hyperglycaemia is common in hospitalized individuals, and is often caused by physiological stress associated with critical illness or major surgery. Insulin therapy is an established treatment for hyperglycaemia and acute hyperkalaemia, and has also been used for myocardial dysfunction resistant to inotropic support. Insulin is commonly used in both organ donors and transplant recipients for hyperglycaemia, but the underlying knowledge base supporting its use remains limited. Insulin therapy plays an important yet poorly understood role in both organ donation and transplantation. Tight glycaemic control has been extensively studied in critical care over the past 15 years; however, this has not yet translated into the field of transplantation, where patients are more unwell and where improved outcomes remain an ongoing challenge. Insulin therapy and optimization of glycaemic control represent important areas for future hypothesis-driven research into organ donation and transplantation, such as amelioration of ischaemia-reperfusion injury, rejection and infection.

KEYWORDS
hyperglycaemia, insulin, organ donation, transplantation

1 INTRODUCTION

Hyperglycaemia, an abnormally high blood glucose level, occurs either because of reduced insulin secretion or reduced hormone sensitivity. It is commonly seen in diabetes mellitus, but can also occur in people without diabetes at times of extreme physiological stress. Stress hyperglycaemia is frequently seen in patients with critical illness, functions as a barometer of physiological response, and is associated with increased morbidity and mortality.\textsuperscript{1}

Organ donors experience severe physiological insults, which lead to either the declaration of brain death or circulatory death following the withdrawal of life-sustaining treatment. Patients who have undergone transplantation surgery are also often at the limits of their physiological reserve and will often require multi-organ supportive...
treatments in a critical care environment. For these reasons, both organ donors and transplant recipients are likely to require insulin to manage glycaemic control, hyperkalaemia or myocardial dysfunction during their inpatient hospital admission. Understanding the physiological effects of insulin therapy in organ donors and transplant recipients is therefore essential to optimize patient outcomes. This review considers the role of insulin therapy in organ donation and transplantation. Medline, EMBASE and Cochrane electronic databases were systematically searched (1980–2018) using the Medical Subject Heading (MeSH) terms: "insulin therapy", "critical care", "organ donation", "transplantation", and "surgery", and these were combined using Boolean operators.

2 | Insulin Therapy and Organ Donation

In organ donors, the process of brain stem death results in the release of catecholamines and initiation of inflammatory processes affecting all organs.1–7 These changes, and potentially the use of corticosteroids in intensive care units (ICUs), lead to hyperglycaemia in ~50% of donors, which is usually managed with insulin.8 Hyperglycaemia stimulates the generation of reactive oxygen species, ultimately leading to inflammation.9 Hyperglycaemia after brain death, may therefore exacerbate the systemic inflammatory response, adversely affecting organ function.

In the United Kingdom, national donor management guidelines suggest a target blood glucose range of between 4.0 and 10.0 mmol/L, and, when glucose levels exceed 10.0 mmol/L, the commencement of an intravenous insulin infusion at a minimum rate of 1 unit per hour.10 High-quality research in this area is limited because variation in practice amongst ICU staff means that it is difficult to determine: a) the extent and duration of hyperglycaemia that is tolerated prior to commencing insulin; b) the precise duration of insulin administration; and c) the triggers for ceasing insulin infusion.

Exogenous insulin requirement during organ donation could be the result of any combination of the following; insulin deficiency caused by underlying diabetes (known or unknown); irreversible β-cell death occurring as a consequence of brain death; reversible β-cell dysfunction caused by short-term metabolic stressors, such as hyperlipidaemia; or insulin resistance caused by inflammation, exogenous steroids and endogenous hormones, such as catecholamines, which are elevated in brain death.

2.1 | Inflammation and brain death

Insulin is also reported to have anti-inflammatory and anti-thrombotic properties through its action on nitric oxide, which leads to a reduction in reactive oxygen species and platelet aggregation via plasminogen activator inhibitor-1.11–14 In a porcine model of brain death, continuous intravenous insulin infusion reduced the expression of pro-inflammatory cytokines (tumour necrosis factor-α [TNF-α] and interleukin [IL]-6) in both the heart and kidney.15 Similar findings were confirmed in 15 brain dead donors (six treated, nine controls) in a randomized controlled trial of insulin using a hyperinsulinaemic-normoglycaemic clamp. In this instance, serum levels of pro-inflammatory cytokines (IL-6 and monocyte chemoattractant protein [MCP]-1) were significantly reduced, whilst the anti-inflammatory cytokine IL-10 was significantly elevated after insulin administration16; however the hyperinsulinaemic-normoglycaemic clamp uses a fixed insulin infusion and a variable glucose infusion, and can be challenging to administer because of the intensive nursing and medical resources required. This may constitute a significant barrier to integrating this intervention into routine clinical practice. A more practical alternative to the hyperinsulinaemic-normoglycaemic clamp is high-dose insulin delivery using a fixed rate glucose-insulin-potassium infusion. Using this mode of insulin delivery intra-operatively, two randomized controlled trials in patients undergoing coronary artery bypass grafting showed reduction in levels of TNF-α, IL-6 and IL-8, and complement factors 3 and 4.17,18

2.2 | Metabolic activity

Hyperinsulinaemic-normoglycaemic clamps using high-dose insulin therapy have been widely used in cardiac surgery and are reported to improve cardiac function and lower levels of anaerobic metabolism in numerous randomized trials.17,19–24 Insulin therapy raises the threshold at which metabolic activity shifts from aerobic to anaerobic processes and results in the reduction of lactate prior to, and after, the ischaemic insult of aortic cross-clamping.23 Directly available cytosolic ATP is also increased after insulin administration, and is believed to confer a protective mechanism by blunting the activation of AMP-activated protein kinases through the phosphorylation of AKT in various cell types.25,26 These findings have not been validated, however, in human organ donors.

2.3 | Donor organ function

The use of insulin in the management of organ donors in intensive care has been considered to be associated with poorer organ function. In one retrospective observational study, data from routine blood samples from 458 organ donors taken at the final stages prior to organ procurement showed that insulin use is associated with a lower glomerular filtration rate (GFR; insulin use vs no insulin use: 77 ± 55 vs 87 ± 59 mL/min/1.73 m²; \( P = 0.009 \)).27

It is unclear from the published literature whether insulin use is a potential marker of the severity of the systemic inflammatory response to brain death or whether poor glycaemic control is the driver behind a potential relationship between insulin use and adverse donor organ function. A more extensive analysis of a larger cohort of kidney transplant recipients (\( n = 1036 \)), where recipients with and without delayed graft function (DGF) were matched 1:1, showed no significant relationship between donor glucose levels and DGF28; however, the relationship between donor insulin use and DGF remains unclear.
2.4 | Donor organ utilization

The relationship between donor insulin use and organ procurement has only been examined on one occasion. Novitzky et al\(^2^9\) analysed data from 40 124 brain-dead donors in the United Network for Organ Sharing (UNOS) registry where they considered the relationship between various combinations of hormone therapies (thyroid hormone, antidiuretic hormone, corticosteroids and insulin) and organ procurement. Donor insulin use was associated with significantly lower rates of pancreas graft procurement, which suggests that donor insulin therapy could be a surrogate marker of donor pancreatic failure. This could be either attributable to pre-existing diabetes (potentially unrecognized and a contra-indication for pancreas transplantation) or because the surgeon considered donor insulin use a marker of β-cell failure secondary to brain death. Crucially, no information about donor characteristics was provided to describe donor phenotypes requiring insulin and why they are less commonly transplanted compared to donors not using insulin. The analysis also did not include data on post-transplantation function and outcomes.

3 | INSULIN THERAPY AND CRITICAL CARE

Intensive insulin therapy to manage hyperglycaemia in the critical care environment came to prominence in 2001 following the seminal publication by Van den Bergh et al.\(^3^0\) In that single-centre randomized trial, 1548 surgical ICU patients received either intensive insulin therapy (aiming for tight glucose control of between 4.4 and 6.1 mmol/L) or conventional treatment (whereby insulin infusion was only commenced if blood glucose values exceeded 11.9 mmol/L, with a target level between 10.0 and 11.1 mmol/L). Intensive insulin therapy resulted in a statistically significant lower mortality rate: 4.6%, vs 8.0% with conventional therapy. The lower mortality rate was most evident in the subgroup of patients with an ICU stay >5 days (20.2% vs 10.6%). That trial included 90 transplant patients, but type of organ transplant received was not reported and the number of deaths was too small to provide a meaningful subgroup analysis.\(^3^0\) In all patients, there was a 46% reduction in blood-borne infections and a 41% reduction in acute renal failure requiring renal replacement therapy.

Van den Bergh et al\(^3^1\) repeated the initial intensive insulin therapy trial in a cohort of 1200 medical ICU patients, but no difference in mortality was seen between the two groups. A 9.5% lower mortality rate was seen in patients receiving insulin among the subgroup of 757 patients who stayed in the ICU for ≥3 days; however, mortality in patients receiving insulin was greater in patients staying <3 days. The authors attributed the beneficial effects to the prevention of acquired kidney injury, earlier weaning from mechanical ventilation and earlier discharge from the ICU in patients who received insulin. Insulin therapy has been demonstrated to prevent cellular hypoxia through its protective effects on the endothelium and mitochondria; this may provide a valuable insight into the potential underlying protective mechanisms of action.\(^3^2,3^3\)

The Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR)\(^3^4\) trial of >6000 patients in an ICU, performed in response to the trials by Van den Bergh et al had conflicting outcomes.\(^3^0,3^1\) NICE-SUGAR did not include any transplant patients but reported an increased mortality in the intervention group (27.5% vs 24.9%; odds of death in the intervention group: 1.14, 95% confidence interval [CI] 1.01 to 1.29). The explanation for the different results may be that, whilst the target blood glucose ranges for the intervention arms of both the NICE-SUGAR and van den Berge trials were similar (4.5–6.0 mmol/L in NICE-SUGAR), the target blood glucose ranges for the conventional treatment arms were different (<10.0 mmol/L in NICE-SUGAR, >10 mmol/L in the van den Berge trials). It is possible that some patients in the conventional treatment arms may have also received insulin therapy to maintain blood glucose levels within the defined parameters for each trial.

After the publications by Van den Bergh et al\(^3^0,3^1\) “tight glycaemic control” for all-comers to ICU was widely adopted, in particular across Europe; however, different approaches to insulin therapy without substrate delivery, as well as a concurrent movement towards early enteral nutrition, may have compounded poor safety profiles of intensive insulin therapy in ICUs, particularly the risk of hypoglycaemia. This was exposed, to some extent, by the conflicting findings of the NICE-SUGAR trial,\(^3^4\) in which participants received eight times less concomitant intravenous glucose than in the initial trial by Van den Bergh et al.\(^3^0\) However, in both trials, the incidence of hypoglycaemia was increased in the intensive insulin therapy arm compared with the standard insulin therapy arm (van den Berge et al: 39 [5.1%] vs 6 [0.8%]; NICE-SUGAR 206 [6.8%] vs 15 [0.5%]). An important message from the NICE-SUGAR trial is that the staff of an ICU should not attempt tight glycaemic control if they are unable to achieve this without increasing the risk of hypoglycaemia. Consequently, tight glycaemic control of critically unwell patients has been largely abandoned, perhaps inappropriately.\(^3^5\)

Intensive insulin therapy is also now an established treatment for the management of profound cardiogenic shock secondary to β-blocker and calcium channel blocker overdose.\(^3^6–3^8\) More recently, the safety, haemodynamic effects and impact on catecholamine dosage of high-dose insulin therapy in patients with inotropic resistant myocardial dysfunction have been demonstrated in critically ill patients without β-blocker and calcium channel blocker overdose.\(^3^9\) In multi-organ donors high-dose catecholamine infusions are commonly required to provide inotropic support and maintain cardiovascular stability, but this can have detrimental effects on organ quality.\(^4^0\) Hormone therapy with insulin infusion may have a role to play in maintaining cardiovascular stability in organ donors without the concomitant adverse effects from catecholamines.

4 | INSULIN THERAPY AND MAJOR SURGERY

Diabetes and dysglycaemia are associated with postoperative morbidity and mortality in patients undergoing major surgery and subsequent
admission to critical care. Optimizing glycaemic control in critical care and defining the parameters of a safe, yet efficacious, target glucose range may be important. Clear guidelines for the use of variable rate intravenous infusion in medical patients exist; however, the paucity of evidence relating to clinical care and outcomes in surgical patients outside of critical care means that optimal care remains poorly defined.

A recent Cochrane review (2012) of peri-operative glycaemic control considered the association of tight glycaemic control with infections, all-cause mortality and hypoglycaemic episodes as primary outcomes. It also examined cardiovascular events, renal failure and length of ICU and hospital stay, health-related quality of life, economic costs, weight gain, and mean blood glucose during intervention as secondary outcomes. Twelve randomized controlled trials were included in the review, with a total of 694 patients randomized to intensive insulin therapy and 709 patients randomized to conventional glycaemic control. The review did not report any improvement in outcomes associated with intensive insulin therapy, although this may reflect the fact that it was underpowered because of a small number of reported events (Table 1).

### 5.1 Liver transplantation

A small cohort of non-diabetic renal transplant recipients reported that patients with poorly controlled glucose (mean glucose > 8.3 mmol/L) had a higher 1-year mortality rate than those receiving insulin therapy with tightly controlled glucose levels in a retrospective case series (48% vs 40%). Such findings have also been confirmed by other studies. When investigated in a randomized controlled trial, insulin therapy was not associated with any difference in DGF between those treated with intensive insulin therapy (21.9% vs 24.7%); however, even the target glucose range was similar in both groups. It is not surprising that no difference was seen between the treatment arms. The evidence regarding the effect of insulin therapy on outcomes in liver transplantation is conflicting, with some studies reporting an increase in graft volume and reduced hepatic dysfunction following insulin treatment, while others have failed to find any benefit.

### 5.2 Renal transplantation

A retrospective case series of 189 liver transplant recipients reported that patients with poorly controlled glucose > 8.3 mmol/L had a higher 1-year mortality rate than those receiving tight glucose control. The review of this evidence suggests that future studies within transplantation but in the absence of robust scientific evidence, should not be directly applied without due regard to the patient's unique clinical circumstances.

| TABLE 1 | Summary of key results of a Cochrane review analysing the association of adverse outcomes with tight peri-operative glycaemic control. |
|----------|-----------------------------------------------------------------------------------------------------------------------------|
| Outcomes | Intensive insulin therapy, n/N | Conventional glycaemic control, n/N | Risk ratio (95% CI) | P value |
| Primary  | 76/638 | 81/637 | 0.83 (0.45–1.52) | 0.54 |
| Infections | 70/629 | 75/629 | 0.83 (0.45–1.52) | 0.54 |
| All-cause mortality | 83/680 | 66/685 | 1.19 (0.89–1.59) | 0.24 |
| Hypoglycaemic episodes | 81/557 | 31/574 | 2.35 (0.87–6.36) | 0.091 |
| Secondary | 114/411 | 113/412 | 0.92 (0.57–1.53) | 0.75 |
| Cardiovascular events | 103 (0.21–5.13) | 103 (5.2–1.52) | 0.83 (0.01–1.52) | 0.54 |
| Renal failure | 108 (3.7–1.53) | 108 (0.27–1.51) | 0.97 |

n/N, number of events/total number of patients exposed.
relationship between glycaemic control and acute rejection in both patients with and without diabetes is similarly conflicting.\textsuperscript{55,57,58}

5.3 \hspace{1em} Islet transplantation

In islet cell transplantation, peri-transplant insulin therapy has been associated with higher rates of insulin independence after islet transplantation but these observational data are far from conclusive regarding clinical benefits of intervention in this setting.\textsuperscript{59,60} Nonetheless, intensive insulin therapy to achieve normoglycaemia in the peri-transplant period has become standard of care. This is partly because islet function is delayed for >10 days after transplantation, and also because there are theoretical benefits in that insulin has been shown to reduce glucotoxicity during the delicate engraftment process.\textsuperscript{61} However, the optimal target blood glucose range in patients after islet cell transplantation remains poorly defined.

5.4 \hspace{1em} Pancreas transplantation

Pancreas transplant is unique in that peri-transplant glycaemic control is influenced by the allograft, whereas for all other types of solid organ transplantation it is influenced by the recipient’s own pancreas and glucose biofeedback. This is particularly relevant as pancreas allograft function is subject to donor factors, including demographics, pre-donation physiology, cold-ischaemia time and ischaemia-reperfusion injury,\textsuperscript{62–65} and recipient factors include demographics, comorbidities, and post-transplantation metabolic changes including the stress response to surgery, infection, diabetogenic immunosuppression (calcineurin inhibitors) and corticosteroid administration.

The paucity of published literature on peri-transplant glycaemic control in solid pancreas transplantation stems, in part, from the low numbers of pancreas transplants performed annually worldwide (circa 2000). Consequently, an inadequate understanding of the relationship between peri-transplant glycaemic control and outcomes makes the definition of graft dysfunction a challenging concept with a lack of uniform or robust adoption.\textsuperscript{65–70} It is unsurprising, therefore, that the rate of reported DGF varies considerably from 0\% to 69\%. One reason to account for the lack of universal uptake of existing DGF definitions is the failure to account for episodes of transient physiological hyperglycaemia, such as stress hyperglycaemia, that may be expected following pancreas transplantation.

6 \hspace{1em} FUTURE TRIALS AND TECHNOLOGIES IN ORGAN DONATION AND TRANSPLANTATION

The existing evidence, predominantly from retrospective series, suggests that glycaemic control is an important area of clinical practice in organ donation and transplantation that requires further research, in particular, randomized trials. It is imperative that future trials address the risks of hypoglycaemia encountered by previous high-profile trials and implement the lessons learnt: these include (1) the co-administration of glucose/substrate with insulin; (2) the utilisation of dynamic insulin infusion protocols that respond to preceding glucose trends and insulin requirement\textsuperscript{71}; (3) glucose ranges broken down into smaller steps leading to smaller incremental changes in insulin rates and smoother trends in glucose levels; (4) adopting wider target glucose ranges (e.g., 4.0–7.0 mmol/L instead of 4.0–6.1 mmol/L) to limit the risks of hypoglycaemia; and (5) utilisation of technology and computation to facilitate close observation of glucose levels and calculate insulin dosing, thereby reducing human error.\textsuperscript{72} The peri-transplant insulin therapy to improve outcomes after pancreas transplantation (PAINTER) trial (ISRCTN 51170824) introduces an intensive insulin therapy protocol which responds to each of these important lessons and seeks to identify whether intensive insulin therapy is safe, effective and acceptable to the transplantation, critical care and diabetes medicine communities.\textsuperscript{73}

Within transplantation, pancreas and islet recipients are likely to benefit from better training in relation to optimal insulin therapy and from greater understanding of the benefits of good glycaemic control. These patients also have an unprecedented opportunity to benefit from technological advances such as continuous glucose monitoring\textsuperscript{74} and closed-loop insulin delivery\textsuperscript{75} introduced within closely monitored and heavily supervised hospital settings. Flash glucose monitoring\textsuperscript{76} boasts high accuracy, user-friendliness and patient engagement, but is not currently licensed for use with insulin sliding scales in hospital settings.

7 \hspace{1em} CONCLUSION

Insulin therapy plays an important yet poorly understood role in both organ donation and transplantation. Tight glycaemic control has been extensively studied, but largely abandoned, in critical care over the past 15 years. However, the potential benefits of insulin have not yet translated into the field of transplantation, where patients are more unwell and where improved outcomes remain an ongoing challenge. The multi-modal effects of insulin therapy that have been demonstrated in both cardiac surgery and critical care offer great promise of translation to transplantation. Insulin therapy could be harnessed to ameliorate ischaemia-reperfusion injury and dampen the inflammatory processes heightened by hyperglycaemia and associated with brain death, and subsequent organ rejection and infection. Pancreas and islet recipients are likely to benefit most from better understanding of insulin therapy and glycaemic control during organ donation and transplantation.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the contribution of the funding organisations: Royal College of Surgeons of Edinburgh and the Medical Research Council (UK).
CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the idea for the article, reviewing and redrafting the article. Iestyn Shapey was the lead author. Iestyn Shapey, Angela Summers and Petros Yiannoulou identified the relevant articles and collected the data. Jonathan Bannard-Smith provided expertise from the perspective of critical care and management of the organ donor. Martin Rutter provided expertise from the perspective of diabetes medicine. Titus Augustine and David van Dellen provided expertise from the perspective of transplant surgery. David van Dellen and Martin Rutter were the senior authors with overall responsibility for the work.

ETHICAL APPROVAL

Ethical approval was not required for the present paper.

ORCID

Iestyn M. Shapey https://orcid.org/0000-0003-3300-1053

REFERENCES

1. Dungan KM, Braithwaite SS, Preiser J-C. Stress hyperglycaemia. Lancet. 2009;373:1798-1807.
2. Bittner HB, Kendall SW, Chen EP, Van Trigt P. Endocrine changes and metabolic responses in a validated canine brain death model. J Crit Care. 1995;10(2):56-63.
3. Chen EP, Bittner HB, Kendall SW, Van Trigt P. Hormonal and homeostatic changes in a validated animal model of brain death. Crit Care Med. 1996;24(8):1352-1359.
4. Maglione M, Ploeg RJ, Friend PJ. Donor risk factors, retrieval technique, preservation and ischemia/reperfusion injury in pancreas transplantation. Curr Opin Organ Transplant. 2013;18(1):83-88.
5. Rech TH, Crispim D, Rheinheimer J, et al. Brain death-induced inflammatory activity in human pancreatic tissue: a case-control study. Transplantation. 2014;97(2):212-219.
6. Contreras JL, Eckstein C, Smyth CA, et al. Brain death significantly reduces isolated pancreatic islet yields and functionality in vitro and in vivo after transplantation in rats. Diabetes. 2003;52(12):2935-2942.
7. Barklin A. Systemic inflammation in the brain-dead organ donor. Acta Anaesthesiol Scand. 2009;53(4):425-435.
8. Geer EB, Islam J, Buettnner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. Endocrinol Metab Clin North Am. 2014;43(1):75-102.
9. Mohanty P, Hamouda W, Garg R, Alijada A, Ghanim H, Danckova P. Glucose challenge stimulates reactive oxygen species (ROS) generation by leucocytes. J Clin Endocrinol Metab. 2000;85(8):2970-2973.
10. Blood and Transplant. Donation after brainstem death (DBD), donor optimisation extended care bundle. 2012. http://www.odt.nhs.uk/pdf/dbd_care_bundle.pdf. Accessed May 13, 2017.
11. Ritchie SA, Ewart M-A, Perry CG, Connell JM, Salt IP. The role of insulin and the adipokines in regulation of vascular endothelial function. Clin Sci. 2004;107:519-532.
12. Trovati M, Anfossi G, Massucco P, et al. Insulin stimulates nitric oxide synthesis in human platelets and, through nitric oxide, increases platelet concentrations of both guanosine-3’, 5'-cylic monophosphosphate and adenosine-3’, 5'-cylic monophosphate. Diabetes. 1997;46(5):742-749.
13. Worthley MI, Holmes AS, Willoughby SR, et al. The deleterious effects of hyperglycaemia on platelet function in diabetic patients with acute coronary syndromes. J Am Coll Cardiol. 2007;49(3):304-310.
14. Stegenga ME, Van Der Crabben SN, Levi M, et al. Hyperglycaemia stimulates coagulation, whereas hyperinsulinaemia impairs fibrinolysis in healthy humans. Diabetes. 2006;55(6):1807-1812.
15. Barklin A, Larsson A, Vestergaard C, et al. Insulin alters cytokine content in two pivotal organs after brain death: a porcine model. Acta Anaesthesiol Scand. 2008;52(5):628-634.
16. Aljiffry M, Hassanain M, Schricker T, et al. Effect of insulin therapy using hyper-insulinemic normoglycemic clamp on inflammatory response in brain dead organ donors. Exp Clin Endocrinol Diabetes. 2016;124(05):318-323.
17. Albacker T, Carvalho G, Schricker T, Lachapelle K. High-dose insulin therapy attenuates systemic inflammatory response in coronary artery bypass grafting patients. Ann Thorac Surg. 2008;86(1):20-27.
18. Visser L, Zuurbier CJ, Hoek FJ, et al. Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: effects on inflammatory response during coronary artery surgery. Br J Anaesth. 2005;95(4):448-457.
19. Ranasinghe AM, McCabe CJ, Quinn DW, et al. How does glucose insulin potassium improve hemodynamic performance? Evidence for altered expression of beta-adrenoreceptor and calcium handling genes. Circulation. 2006;114(Suppl. 1):239-1-244.
20. Ranasinghe AM, Quinn DW, Pagano D, et al. Glucose-insulin-potassium and tri-iodothyronine individually improve hemodynamic performance and are associated with reduced troponin I release after on-pump coronary artery bypass grafting. Circulation. 2006;114(Suppl. 1):245-251.
21. Howell NJ, Ashrafian H, Drury NE, et al. Glucose-insulin-potassium reduces the incidence of low cardiac output episodes after aortic valve replacement for aortic stenosis in patients with left ventricular hypertrophy: results from the hypertrophy, insulin, glucose, and electrolytes (HINGE) trial. Circulation. 2011;123(2):170-177.
22. Quinn DW, Pagano D, Bonser RS, et al. Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: a randomized controlled trial. J Thorac Cardiovasc Surg. 2006;131(1):34-42.
23. Albacker TB, Carvalho G, Schricker T, Lachapelle K. Myocardial protection during elective coronary artery bypass grafting using high-dose insulin therapy. Ann Thorac Surg. 2007;84(6):1920-1927.
24. Carvalho G, Pelletier P, Albacker T, et al. Cardioprotective effects of glucose and insulin administration while maintaining normoglycemia (GIN therapy) in patients undergoing coronary artery bypass grafting. J Clin Endocrinol Metab. 2011;96(5):1469-1477.
25. Klein LJ, Visser FC. The effect of insulin on the heart: part 2: effects on function during and post myocardial ischaemia. Neth Heart J. 2010;18(5):255-259.
26. Mankad P, James A, Siriwardena AK, Elliott AC, Bruce JE. Insulin protects pancreatic acinar cells from cytosolic calcium overload and inhibition of plasma membrane calcium pump. J Biol Chem. 2012;287(3):1823-1836.
27. Blasi-Ibanez A, Hirose R, Feiner J, et al. Predictors associated with terminal renal function in deceased organ donors in the intensive care unit. Anesthesiology. 2009;110(2):333-341.
28. Olmos A, Feiner J, Hirose R, et al. Impact of a quality improvement project on deceased organ donor management. Prog Transplant. 2015;25(4):351-360.
71. Vogelzang M, Ligtenberg JJ. Practical aspects of implementing tight glucose control in the ICU. Curr Opin Clin Nutr Metab Care. 2007;10 (2):178-180.
72. Higgs MH, Fernandez RS. Computerised insulin dosing calculators for the management of continuous insulin infusions after cardiac surgery: a systematic review and meta-analysis. Intensive Crit Care Nurs. 2017; 39:37-44.
73. Shapey IM, Summers A, Bannard-Smith J, Augustine T, Rutter MK, van Dellen D. Peri-transplant insulin therapy to improve outcomes in pancreas transplantation (PAINTER): an open label randomised controlled trial. http://www.isrctn.com/ISRCTN51170824. 2019. Accessed April 5, 2019.
74. Mittal S, Franklin RH, Policola C, Sharples E, Friend PJ, Gough SCL. Early postoperative continuous glucose monitoring in pancreas transplant recipients. Transpl Int. 2015;28(5):604-609.
75. Forlenza GP, Nathan BM, Moran AM, et al. Successful application of closed-loop artificial pancreas therapy after islet autotransplantation. Am J Transplant. 2016;16(2):527-534.
76. Leelarathna L. Wilmot EG. Flash forward: a review of flash glucose monitoring. Diabet Med. 2018;35(4):472-482.

How to cite this article: Shapey IM, Summers A, Yiannoullou P, et al. Insulin therapy in organ donation and transplantation. Diabetes Obes Metab. 2019;21:1521-1528. https://doi.org/10.1111/dom.13728