ASSOCIATION OF BRITISH CLINICAL DIABETOLOGISTS AND RENAL ASSOCIATION GUIDELINES ON THE DETECTION AND MANAGEMENT OF DIABETES POST SOLID ORGAN TRANSPLANTATION

Tahseen A Chowdhury MD, FRCP, Consultant in Diabetes, Royal London Hospital, London

Mona Wahba MA, FRCP, Consultant Nephrologist, St Helier Hospital, Carshalton

Ritwika Mallik MBBS, DNB, MRCP(UK), Specialist Registrar in Diabetes, Royal London Hospital, London

Javeria Peracha MB ChB, MRCP (UK), Specialist Registrar in Nephrology, University Hospitals Birmingham NHS Trust

Dipesh Patel PhD, FRCP, Consultant Physician, Diabetes & Endocrinology, Royal Free NHS foundation Trust, Honorary Associate Professor, UCL

Parijat De MBBS, MD, FRCP, Consultant Diabetologist, City Hospital, Birmingham

Damian Fogarty BSc, MD, FCRP, Consultant Nephrologist, Belfast Health and Social Care Trust, Belfast

Andrew Frankel MD, FRCP, Consultant Nephrologist, Imperial College Healthcare NHS Trust, London

Jannaka Karraliede MBBS, FRCP, PhD, Consultant Diabetologist Guys and St Thomas's NHS Foundation Trust, London

Patrick B. Mark MB ChB, PhD, Professor of Nephrology, University of Glasgow, Glasgow

Rosa M Montero MD (Res), MRCP, Consultant Nephrologist, Royal Berkshire NHS Foundation Trust, Reading

Ana Pokrajac MD, MSc, FRCP, Consultant Diabetologist, West Hertfordshire Hospitals NHS Trust, Watford

Sagen Zac Varghese FRCP (Endo), PhD, FHEA, MEd, Consultant Diabetologist, ENHIDE, Lister Hospital, Stevenage

Stephen C Bain MA, MD, FRCP, Professor of Medicine (Diabetes), University of Swansea, Swansea

Indranil Dasgupta DM, FCRP, Consultant Nephrologist, Heartlands Hospital, Birmingham. Warwick Medical School, Warwick

Debasish Banerjee MD FHEA FASN FRCP, Consultant Nephrologist, Renal and Transplant Unit, St George's University Hospital NHS Foundation Trust, London

Peter Winocour MD, FRCP (Glas), FRCP (Lond), Consultant Diabetologist, ENHIDE, QE2 Hospital, Welwyn Garden City

Adnan Sharif MD, FRCP, Consultant Nephrologist, University of Birmingham

Correspondence

Tahseen A Chowdhury

Consultant in Diabetes, The Royal London Hospital, Whitechapel, London E1 1BB

Email: tahseen.chowdhury@nhs.net

Phone: +44 0208 223 8384

ABSTRACT

Post-transplant diabetes mellitus (PTDM) is common after solid organ transplantation (SOT) and associated with increased morbidity and mortality for allograft recipients. Despite the significant burden of disease, there is a paucity of literature with regards to detection, prevention and management. Evidence from the general population with diabetes may not be translatable to the unique context of SOT. In light of emerging clinical evidence and novel anti-diabetic agents, there is an urgent need for updated guidance and recommendations in this high-risk cohort. The Association of British Clinical Diabetologists (ABCD) and Renal Association (RA) Diabetic Kidney Disease Clinical Speciality Group have undertaken a systematic review and critical appraisal of the available evidence. Areas of focus are; 1) Epidemiology, 2) Pathogenesis, 3) Detection, 4) Management, 5) Modification of immunosuppression, 6) Prevention, and 7) PTDM in the non-renal setting. Evidence-graded recommendations are provided for the detection, management, and prevention of PTDM, with suggested areas for future research and potential audit standards. The guidelines are endorsed by Diabetes UK, the British Transplantation Society and the Royal College of Physicians of London. The full guidelines are available freely online for the diabetes, renal and transplantation community using the link below. The aim of this review article is to introduce an abridged version of this new clinical guideline.

https://abcd.care/sites/abcd.care/files/site_uploads/Resources/Position-Papers/ABCD-RA%20PTDM%20v14.pdf.

Evidence grades for the recommendations

The following evidence grading has been used to determine the strength of the recommendations; the suggested audit standards; and the questions for areas that require future research.

1A – Strong recommendation: high-quality evidence

1B – Strong recommendation: moderate-quality evidence

1C – Strong recommendation: low-quality evidence

1D – Strong recommendation: very low-quality evidence

2A – Weak recommendation: high-quality evidence

2B – Weak recommendation: moderate-quality evidence

2C – Weak recommendation: low-quality evidence

2D – Weak recommendation: very low-quality evidence

Search strategy

The recommendations are based on a systematic review of the Cochrane Library, PubMed/MEDLINE, Google Scholar and Embase, using the following key words: new onset diabetes after transplantation, post-transplant diabetes, renal transplant and diabetes, liver transplant and diabetes, cardiac transplant and diabetes, lung transplant and diabetes.

INTRODUCTION

Solid organ transplantation (SOT) for people with end organ failure is a well-established and life-saving treatment. Whilst diabetes mellitus (DM) is recognised as the most important cause of kidney failure worldwide [1], high-risk for development of post-transplant dysglycaemia has been recognised for decades. Post-Transplant Diabetes Mellitus (PTDM), previously termed New Onset Diabetes after Transplantation (NODAT), is common in people undergoing SOT, and associated with adverse clinical outcomes.

Due to generic and transplant-specific risk factors, PTDM should be considered as a distinct pathophysiological entity. The aim of this guideline is to focus specifically on dysglycaemia or DM recognised primarily *after* transplantation. We recognise, however, many such people may have undetected pre-transplant DM. Indeed, the term NODAT was changed to PTDM by a Consensus report in 2014, to reflect time of diagnosis rather than time of onset [2]. We focus on renal transplantation but include some data on other SOT where available. While these recommendations focus on PTDM, they are relevant for SOT recipients with pre-existing diabetes who are likely to suffer glycaemic deterioration post-transplantation. The management of DM following the failing/failure of the pancreas in simultaneous pancreas-kidney transplants is not addressed in these guidelines.

1. EPIDEMIOLOGY OF PTDM (see Box 1)

Incidence and prevalence of PTDM

Prior to a 2003 Consensus report [3], reported incidence and prevalence of PTDM varied significantly and reflected heterogenous clinical practice. Different immunosuppressive regimens, mixed diagnostic criteria and diverse transplant cohort demographics meant reported incidence and prevalence rates were not comparable [4]. The 2003 consensus meeting formulated guidelines on diagnosis, prevention and management of PTDM [3]. Reported incidence of PTDM varies between 9% and 39% in the first-year, and likely reflects distinct patient demographics and immunosuppression practice [5]. Beyond the first year, it is difficult to determine whether the incremental risk of developing PTDM is over and above the incremental risk of developing diabetes in the general population. With increasing longevity of both transplant recipients and their allograft, the presumption is that the cumulative exposure to diabetogenic risk factors (both traditional and transplant-specific) leads to continued risk for PTDM [6].

Some studies suggest that the incidence of PTDM is declining, possibly due to rationalised immunosuppression or reduced rejection. Contemporary immunosuppression regimens adopt calcineurin inhibitor (CNI) sparing regimens (to avoid the risk of nephrotoxicity), and this reduced exposure may reduce the risk of PTDM. In a Norwegian single-centre analysis, the odds of developing PTDM appear to have halved between 1997 and 2007 [7].

Impact of PTDM on long-term patient/graft outcomes

Some studies suggest that PTDM is associated with increased risk of mortality after transplantation [8-10], although this is not consistently reported [11]. The lack of robust data collection by national transplant registries for PTDM is a major factor limiting the accurate assessment of the impact of PTDM on mortality.

The association between PTDM and graft loss is unclear. While an association with overall graft loss is well recognised (driven by mortality), the association between PTDM and death-censored graft loss is uncertain [10]. United States Renal Data System (USRDS) registry observed a similar impact of PTDM and acute rejection on the risk for overall graft loss due to different mechanisms; PTDM was associated with increased risk for mortality but not death-censored graft loss [12]. The worst overall outcome existed for people who developed both rejection and PTDM [13]. One study observed an association between PTDM and overall graft loss but not death-censored graft loss [14]. In a large prospective cohort, increased graft loss with PTDM related to patient death rather than death-censored graft loss [15].

Impact of PTDM on morbidity

Rejection remains the leading cause of patient concern, but the relationship between PTDM and rejection may not be bi-directional. Treatment for allograft rejection includes corticosteroid boluses, which increases risk for PTDM, but it is unclear if PTDM leads to an increased risk for rejection, (although pre-existing diabetes appears to increase this risk) [16].

A number of studies have shown an association between PTDM and increased risk of cardiovascular disease (CVD) [17,18]. While this risk may not be as high in those with pre-existing diabetes, it likely reflects the difference in cumulative exposure to glycaemia, or the presence of metabolic syndrome. In addition, pre-diabetes has been suggested as a risk factor for the development of CVD in people with PTDM [19].

Data on PTDM and risk of microvascular complications are limited. One study observed the emergence of diabetes-related microvascular complications within three years in over half of kidney transplant recipients who developed PTDM [20]. Here, the median time to onset of microvascular complications was 1.8 years, which is short compared with non-transplant diabetes. This contrasts with more recent data from 64 people with PTDM of at least 5-years duration, who had a lower than expected prevalence of microvascular complications, with little evidence of retinopathy, but higher prevalence of neuropathy [21]. In people with diabetes undergoing renal transplantation, diabetic nephropathy can recur [22]. In people with PTDM, development of de novo diabetic nephropathy seen on renal biopsy has been reported in 8 out of 81 people with diabetes [23].

2. PATHOGENESIS OF PTDM (see Box 2)

PTDM may be considered a distinct metabolic entity from other forms of diabetes and its pathogenesis reflects this separation. Risk factors for PTDM can be categorised as non-modifiable versus modifiable, or generic versus transplant-specific (Table 1). Knowledge of PTDM risk factors is evolving. For example, data are conflicting with regards to whether adult polycystic kidney disease (APKD) is a risk factor for PTDM, with published studies showing positive and negative associations [24-25]. Understanding PTDM risk factors is important to help risk stratify and counsel transplant recipients, facilitate additional support or consider pre-emptive modification to attenuate PTDM risk.

PTDM develops in the context of declining insulin secretion, in the presence of insulin resistance, and is supported by mechanistic research [7]. However, both general and transplant-specific risk factors influence pathophysiology. For example, CNIs are strongly linked to PTDM [26], and associated with decreased insulin sensitivity in the context of diminished insulin secretion [27]. Tacrolimus trough level reduction is shown to improve β-cell secretion, suggesting the diabetogenic risk of CNIs is dose-

dependent. CNIs up-regulate insulin gene expression and decrease insulin synthesis by transcriptional inhibition of insulin mRNA [28], and may also affect insulin secretion through reversible toxicity to the β-cell [29]. This effect appears to be strongest in people with high triglycerides (i.e. with metabolic syndrome) [30] and may be due to an interaction between tacrolimus and free fatty acids in the β-cell leading to β-cell dysfunction [31].

The role of glucocorticoids in the development of PTDM relates to their interference with carbohydrate metabolism and insulin secretion/action via a number of mechanisms, including inducing insulin resistance by downregulating insulin receptors in liver, muscle and adipose tissue. Recent work from genome-wide association studies supports the hypothesis that β–cell dysfunction is critical in the development of PTDM, with a number of single-nucleotide polymorphisms identified in genes that are associated with β-cell apoptosis [32].

The current consensus is that β–cell dysfunction is the dominant pathophysiological defect in early PTDM, with insulin resistance the major contributor later in the condition.

3. DETECTION OF PTDM (see Box 3)

Consensus guidelines for PTDM have aligned themselves with ADA recommendations [2], and emphasise the clinical relevance of pre-diabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]). Pre-diabetes is a risk factor for development of PTDM, and IGT *per se* may be an independent predictor of mortality [33].

Although early post-operative hyperglycaemia commonly occurs after renal transplantation, this may be a risk-factor for subsequent development of PTDM and it should not be used as a diagnostic criterion since many cases are transient. Diagnosis should be made in a stable clinical period, at least six weeks after transplantation [2].

Fasting plasma glucose (FPG)

FPG ≥7.0 mmol/L (126 mg/dL) is a criterion for the diagnosis of DM, although requires more than one abnormal value in the absence of symptoms [60]. IFG is defined by the ADA as FPG 5.6-6.9 mmol/L, and the World Health Organisation (WHO) as 6.1-6.9 mmol/L.

FPG is a relatively easy screening method for glucose homeostasis alterations but has several limitations. Isolated elevation of FPG is a consequence of hepatic insulin resistance with normal muscle insulin sensitivity, often combined with defects in early-phase insulin secretory response [34]. In non-transplanted subjects, IFG is more common in men than in women, with minimal overlap with IGT. In stable kidney transplant recipients without a known history of diabetes, the prevalence of

isolated IFG has been reported to be 12-18%, isolated IGT in 9% and combined IFG/IGT in 12-14% [35]. In both general and transplant populations, sole determination of FPG would miss a third of people with PTDM who have an isolated defect in glucose tolerance [35]. Normal FPG in people with IGT may occur in renal disease due to reduced renal clearance of insulin.

Some transplant centres have reported hybrid approaches, combining diagnostic tools (e.g. OGTT) stratified by threshold FPG level [36]. During the first 4-6 weeks after transplantation, FPG alone is of low value to detect hyperglycaemia, but despite these limitations, people with high FPG values have poorer outcomes in graft and patient survival [37].

2-hour plasma glucose during OGTT

OGTT is widely accepted as the gold standard for diagnosis of PTDM and remains the diagnostic test of choice in PTDM guidelines [2]. Disadvantages include poor reproducibility and logistical obstacles for routine use, suggesting it should be reserved for use in specific situations where diagnostic clarification of PTDM is essential.

Glycated haemoglobin (HbA_{1c})

Since the adoption of HbA_{1c} as a diagnostic tool for DM in 2009 [38], the utility of HbA_{1c} in the diagnosis of PTDM has been debated. Falsely high HbA_{1c} levels can be observed with acidosis [39] and iron deficiency [40], while falsely low HbA_{1c} levels can result from blood loss, blood transfusions, shortened erythrocyte survival time and erythropoietin [40]. During the first year after kidney transplantation, anaemia may be present in 50%.

Prospective long-term data using HbA_{1c} as a diagnostic tool for PTDM with analysis of macro- and microvascular complications are lacking, but several smaller studies have explored the utility of HbA_{1c} post kidney transplantation. Some have shown better sensitivity than FPG [41], good concordance with OGTT results [42] and 83% sensitivity for detection of PTDM with cut-off $\geq$5.8% to avoid need for OGTTs [36]. HbA_{1c} is of poor diagnostic value in the first three months due to anaemia, but predicts risk of pre-diabetes and PTDM at 1- and 3-years after kidney transplantation [43]. Some studies suggest that HbA_{1c} may detect PTDM only in a minority of cases detected by OGTT [44]. Early use of HbA_{1c} was shown to be highly specific but poorly sensitive to diagnose PTDM in a recent meta-analysis [45]. HbA_{1c} measurement may therefore be considered in stable kidney transplant recipients for the detection of transplant associated hyperglycaemia and PTDM beyond three months after transplantation, ideally in combination with FPG. Whilst certain caveats in comparison to OGTT exist, its ease of use makes it an attractive diagnostic tool.

Continuous glucose monitoring (CGM)

CGM devices offer the ability to obtain glucose profiles over days and weeks and aid understanding of post-transplant hyperglycaemia. CGM monitoring has shown people with T2D demonstrate higher glycaemic variability (GV) than people with PTDM [46] and detects hyperglycaemic episodes that would have remained undetected by routine laboratory testing [47,48]. CGM may therefore be useful in the detection of early postoperative hyperglycaemia as FPG may be normal, HbA_{1c} unreliable and OGTT impractical.

Fructosamine and glycated albumin

Fructosamine and glycated albumin are alternative measures for glycaemia but their link to average glucose and their prognostic significance are less clear. Fructosamine correlates with glycaemic control during the previous 1-3 weeks. Determination of fructosamine as an index of diabetic control has not shown any benefit in the care of diabetes people over blood glucose and HbA_{1c} monitoring [49], and is thus, usually used in situations where HbA_{1c} is unreliable. The paucity of data related to fructosamine or glycated albumin means their standard use cannot be recommended currently.

4. MANAGEMENT OF PTDM (see Box 4)

Distinct categories of hyperglycaemia may be seen following organ transplantation, including pre-existing diabetes (sometimes previously undetected), transient hyperglycaemia in the early post-operative period, and persistent PTDM [50]. Treatment of dysglycaemia post transplantation can be divided into treatment of acute hyperglycaemia in the early post-operative period, and longer-term treatment once renal function and immunosuppression is more stable (usually at around three months post-transplant). A suggested pathway for glycaemic management of PTDM is shown in figure 1.

Early post-operative hyperglycaemia and glucose management in hospital

Dysglycaemia in the early post-operative period following transplantation is secondary to a constellation of aetiological factors. It is frequent and has been associated with poor outcomes including risk for long-term PTDM, rejection, infection, delayed graft function, graft loss and death [S1].

Corticosteroids are important during induction of immunosuppression, and early post-transplant hyperglycaemia shares some similarities with steroid-induced diabetes. The Joint British Societies Guidelines on the Management of Hyperglycaemia and Steroid Therapy offer consensus-based guidelines on glucose management with corticosteroids [S2]. Post-transplant hyperglycaemic emergencies do occur, and exclusion of diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome is important. Significant hyperglycaemia (glucose $\geq$ 14.0 mmol/L) should be managed

actively with subcutaneous insulin (if patient is eating and drinking) or variable rate intravenous insulin infusion, intravenous fluids and hourly blood glucose monitoring. Lower levels may be managed with oral hypoglycaemic agents. In similar in-patient settings, such as myocardial infarction or intensive care, there is no evidence to support very tight glucose control and there is even some suggestion of harm [S3]. Once the patient is stabilised, conversion from intravenous to subcutaneous insulin should be undertaken, usually to a once-daily isophane insulin [why not longer acting once-daily insulin?] (preferably given in the morning), with additional prandial insulin as needed.

Glycaemic targets in PTDM

Active monitoring of glucose control is important after transplantation. Some observational studies suggest poorer graft outcomes with poorer control. A Korean study of 3538 kidney transplant recipients suggested that the highest quartile of time-averaged glucose was related to poor graft outcomes (graft failure or death) [S4]. A further cohort study of 798 renal transplant recipients showed that being in the highest quartile of maximal glucose increased the adjusted risk of death by a factor of 2.2 [S5]. In the absence of clinical evidence showing improved PTDM outcomes with better glucose control, however, targets used in T2D are probably appropriate for people with PTDM. The American Diabetes Association (ADA) suggests an overall glucose target of 7.0% (53 mmol/mol), but less stringent targets may be appropriate [S6]. KDIGO recommends a glycaemic target of 7-7.5% (53-58 mmol/mol) after renal transplantation [S7]. The ABCD-RA guidelines on managing hyperglycaemia in people with diabetes and diabetic nephropathy-chronic kidney disease suggest less stringent targets according to grade of CKD; we believe that these should apply to PTDM [S8] (Table 2).

Glucose lowering therapies in PTDM

As the therapeutic armamentarium for management of hyperglycaemia increases, a number of newer therapies are available to manage glucose in PTDM. Many have not been adequately tested in PTDM and a personalised approach is warranted. Risk of interaction with immunosuppressants should be considered [S9]. For example, ciclosporin inhibits cytochrome P450 3A4 enzyme, and may increase levels of prandial glucose regulators, gliptins, sulfonylureas and possibly sodium-glucose transporter-2 (SGLT-2) inhibitors .

Diet and lifestyle-based management

Weight gain is common following transplantation, and dietetic input for transplant patients is important [S10]. In one study of 33 people randomised to intensive versus standard dietary intervention, weight gain was limited to 5.5kg in the intensive group, compared to 11.8kg in the standard group [S11]. Higher weight pre-transplantation is a risk factor for PTDM and should be a target for prevention.

A clinical trial of dietitian delivered active versus passive lifestyle intervention in 130 renal transplant recipients showed no change in glycaemic indices of metabolism but did demonstrate reduction in fat mass and weight, and possibly a reduced incidence of PTDM, which did not reach significance (7.6% v 15.6%, p=0.123) [S12]. A prospective study of 468 renal transplant recipients showed that a Mediterranean diet was associated with lower PTDM risk [S13].

Oral hypoglycaemics

Metformin

In the post-transplant setting, metformin should be considered for management of PTDM if renal function allows, with appropriate dose adjustment (reduced to 500mg twice daily in eGFR $\leq$45 mls/min/1.73m^2 and stopped if eGFR falls $\leq$30 mls/min/1.73m^2). In a large US survey of 14,144 renal transplant recipients, 4.7% received metformin within 12 months post-transplant, and they had significantly lower all-cause, malignancy-related and infection-related mortality [S14]. In a further observational study of 46,914 transplant recipients, <10% received metformin, but they had better transplant survival and lower mortality [S15]. Selection bias for people with better renal function being prescribed metformin may have contributed to these findings.

Metformin is first line therapy for treatment of T2D in many guidelines and has been suggested as a potential first line agent for treatment of PTDM [S16]. In transplant patients with stable renal function and no other contraindications, metformin should be encouraged.

Sulfonylureas/Meglitinides

Due to their rapid efficacy and ease of administration, sulfonylureas are commonly used in people with PTDM with limited clinical efficacy data [S17]. Repaglinide has been shown to lower HbA_{1c} in a small observational study [S18]. Whilst useful in the early post-transplant period, both classes must be balanced with the risk of hypoglycaemia, particularly when immunosuppressive regimes are being titrated.

Glitazones

Glitazones have been shown to be safe and effective in small studies of people with PTDM. In one study of 10 patients treated with insulin or glyburide post-transplant, the addition of pioglitazone lowered HbA_{1c} by 1.4% (12 mmol/mol) and reduced the dose of insulin [S19]. A study of non-diabetic renal transplant recipients randomised to pioglitazone or placebo showed a modest benefit in carotid intima-media thickening [S20]. In a further study of 40 people with PTDM initially stabilised with insulin, adding rosiglitazone at three months post-transplant led to only 3/40 subsequently requiring insulin [S21]. Glitazones may be useful to treat liver steatosis post liver transplant [S22]. Fluid retention, weight gain and increased fracture risk limit their use.

Dipeptidylpeptidase-4 (DPP-4) inhibitors (gliptins)

Gliptins are useful in people with PTDM as they have few side effects, although they have modest efficacy. A number of unrandomized, small scale, short duration studies have reported the use of gliptins in PTDM. A meta-analysis of five gliptin studies in PTDM suggested an approximate 1% (11 mmol/mol) reduction in HbA_{1c}, with no effect on eGFR [S23].

Glucagon-like Peptide-1 (GLP-1) analogues

GLP-1 analogues are increasingly used in CKD. In the largest reported cohort in SOT (n=63), patients treated with dulaglutide showed a mean weight reduction at two years of 5.23kg, insulin dose reduction of 5.94 units, although no significant improvement in glycaemic control was seen [S24].

Sodium Glucose Transporter-2 (SGLT-2) inhibitors

SGLT-2 inhibitors are accruing significant clinical evidence for cardio- and reno-protection in the non-transplant setting [S25]. In PTDM, potential side effects (genito-urinary infection or euglycaemic ketoacidosis) are a concern. In a placebo-controlled study (n=44), a modest reduction in HbA_{1c} of 0.2% (2mmol/mol) was seen with reduced weight and no difference in adverse events [S26]. No cardiorenal protection data are available in PTDM.

Insulin

There is no randomised study of insulin regimens in PTDM. As early post-operative hyperglycaemia may be managed with once-daily NPH insulin, this seems the regimen of choice for most people, particularly as it may usefully reduce postprandial hyperglycaemia which is typical of steroid induced hyperglycaemia. As steroid doses are weaned, insulin doses must be carefully titrated. Longer term, insulin therapy may be required in PTDM, and standard regimens such as basal insulin, twice-daily fixed mixtures or basal bolus regimens may be used.

<u>Management of cardiovascular risk factors in people with PTDM</u>

Cardiovascular disease (CVD) remains a significant problem after SOT [S27]. As PTDM increases this risk, cardiovascular risk reduction is important, although traditional cardiovascular risk factors may not be highly predictive of cardiac events [S28]. Smoking cessation, however is mandatory, as there is a high risk of allograft failure in smokers compared to non-smokers, and smoking may increase the risk of PTDM [S29].

Dyslipidaemia is common amongst people undergoing transplantation. The Assessment of LEscol in Renal Transplantation (ALERT) study randomised over 2,100 low-risk renal transplant recipients to fluvastatin or placebo, and despite a 32% reduction in LDL cholesterol, no significant difference in major adverse cardiovascular events (MACE) was seen [S30]. A Cochrane meta-analysis of 17 studies of statin use in renal transplant recipients showed non-significant reductions in MACE (RR 0.84, 95%

CI 0.66–1.06), cardiovascular death (RR 0.68, 95% CI 0.45–1.01), and myocardial infarction (MI - RR 0.70, 95% CI 0.48–1.01) [S31]. Nevertheless, KDIGO guidelines suggest statin therapy for all renal transplant recipients [S7], aiming for a target LDL cholesterol below 100mg/dl (2.6 mmol/L).

Hypertension is common post transplantation and, if uncontrolled, associated with adverse graft outcomes. Unlike CKD settings, renin-angiotensin aldosterone system (RAAS) blockers lack evidence for improved outcomes. There is some suggestion that calcium channel blockade may be beneficial in hypertension post transplantation [S32]. There is currently no strong evidence for the optimum BP target for renal transplant recipients. KDIGO guidelines suggest a target BP of 130/80 mmHg [S7], which concords with the target of 130/80 mmHg in people with diabetic kidney disease [S33].

Structured diabetes care and screening for diabetes complications

There may be a lower rate of microvascular complications in PTDM versus people with T2D, but in those who develop complications, progression may be accelerated, justifying regular surveillance. All people with PTDM should therefore be registered in a primary care diabetes register, and receive standard screening and management within primary care. Close liaison with the transplant team, however, will be required when additional therapy for glucose or cardiovascular risk factors is warranted. In large transplant centres, PTDM may be effectively managed in a multi-disciplinary clinic involving diabetes and renal specialists.

5. MODIFICATION OF IMMUNOSUPPRESSION TO PREVENT OR TREAT PTDM (see Box 5)

Immunosuppressive therapy used in SOT includes induction therapy (antithymocyte globulin (ATG), basiliximab and alemtuzumab) and maintenance therapy (corticosteroids, CNIs, azathioprine, mycophenolate mofetil [MMF], mTOR inhibitors (sirolimus and everolimus), and belatacept.

Contemporary guidance advocates choosing immunosuppression to prolong patient/graft survival rather than prevention of PTDM [S34]. Immunosuppression should be personalised to each patient for stratified risk/benefit and it is notable that protocols in the UK are heterogenous between transplant units. The diabetogenic potential for various immunosuppressive drugs is shown is Table 3.

Corticosteroids

There is debate on risk/benefit of corticosteroid-sparing regimens post-transplantation. Some RCTs show no effect of steroid-sparing regimens on PTDM incidence, whilst others have shown reduced PTDM (references?). Steroid sparing regimens may involve either rapid reduction of steroid dose, or complete cessation within a short timescale. In a meta-analysis of 34 studies (n=5,637), steroid sparing regimens after kidney transplantation were associated with lower risk for PTDM, higher risk for rejection, worse graft function and equivalent patient/graft survival [S35]. By contrast, however, some studies have shown no increase in acute or chronic rejection rates with steroid-free regimens. One such study (n=25,837) was associated with reduced odds of developing PTDM within three years [S36]. With 15-year follow up, retrospective analysis of 1,553 kidney transplant patients suggested rapid discontinuation of steroids was associated with reduced onset of PTDM without any impact on graft function or patient/graft survival [S37]. Two recent RCTs, Harmony (n=615) and ADVANCE (n=1081) both showed reduced PTDM with steroid-sparing regimens with no increase in rejection [S38, S39].

These discrepant findings may be explained by the diabetogenic effects of CNIs reducing any potential benefits of steroid-sparing regimens. It is also possible high CNI trough levels are responsible for the absence of beneficial effects of steroid-sparing on incidence of PTDM. In view of continued uncertainty, further research in this area is warranted.

Calcineurin inhibitors

CNIs increase risk for PTDM, with tacrolimus showing greater diabetogenic risk than ciclosporin [26]. In an open-label, multicentre RCT, tacrolimus-based immunosuppression with steroid maintenance was found to provide the best balance between PTDM and acute rejection (compared to ciclosporin or steroid avoidance) [S40]. The authors suggested tacrolimus-to-ciclosporin conversion in people with inadequately controlled PTDM after the early phase post-transplantation may be considered.

A more recent tacrolimus-to-ciclosporin conversion RCT (n=80) found 39% of people in the ciclosporin arm were off glucose-lowering medication versus 13% in the tacrolimus arm at 12 months (p=0.01) [S41]. Risk for rejection was not increased, but ciclosporin conversion was associated with reduced renal function. Economic evaluation suggested ciclosporin offered the second-best net health benefit after immediate release-tacrolimus for people at risk of complications from diabetes, and some advocates support this strategy [S42].

CNI-sparing is a further strategy to reduce risk of PTDM, but meta-analyses give conflicting results [S43, S44].

mTOR inhibitors

A meta-analysis including 33 trials (n=7114 renal transplant recipients) observed no differences in incidence of PTDM with mTORi [S45]. Large registry analysis showed sirolimus increases risk of PTDM, with the most diabetogenic combination being concomitant CNI use [S46]. A recent meta-analysis exploring conversion from CNI to everolimus included 11 RCTs (n=1633), and observed lower incidence of PTDM (4.92% vs 8.29%, p=0.16), but increased risk for rejection at 1-year (risk ratio 1.82 [1.11–2.99]) [S47].

An RCT including 613 renal transplant recipients showed everolimus plus low-dose tacrolimus facilitates reduced CNI exposure, while achieving good renal function, low graft loss, with similar incidence of hyperglycaemia at 12 months (24.8% versus 27.0%) [S48].

Other agents

Belatacept blocks CTLA-4, leading to selective blockade of T-cell activation. It has been shown in a RCT to reduce incidence of PTDM compared to ciclosporin [S49]. In a meta-analysis of RCTs (n=1535), belatacept-based immunosuppression had equivalent patient/graft survival but less kidney scarring and reduced risk for PTDM [S50]. When compared to tacrolimus-based regimens, belatacept has less risk for PTDM. Cost and logistical issues with parenteral administration has limited wider use of belatacept.

Observational data have suggested that basiliximab (a monoclonal antibody to CD25) is associated with PTDM, while meta-analyses do not identify any association [S51].

6. PREVENTION OF PTDM (see Box 6)

Lifestyle intervention

Prevention or delay of T2D is feasible using lifestyle intervention or pharmacotherapy [S52]. More recently, remission of T2D has been achieved in people treated with very low-calorie diets [S53]. PTDM has additional risk factors that may be modifiable (e.g. immunosuppression). Lifestyle intervention for prevention of PTDM has been discussed in section 4.

Bariatric surgery has a potent effect on prevention (or remission) of T2D in high-risk people. In haemodialysis patients, there may be a role for bariatric surgery to prevent development of PTDM. In one series of 24 haemodialysis patients undergoing bariatric surgery, pre-operative BMI mean was 41 kg/m^2, and dropped to a mean of 28 kg/m^2, facilitating transplantation in 16 people [S54].

Pharmacological intervention

In the non-transplant setting, a number of pharmacological agents have been shown to prevent or delay the onset of T2D high-risk individuals. Amongst renal transplant recipients, a study of 48 people with stable renal transplants and IGT treated with 3-months of vildagliptin or pioglitazone led to a significant reduction in 2-hour glucose, although no wash out period was used in this study, so prevention of PTDM was not established [S55]. Studies are planned using metformin and gliptins to prevent PTDM.

In a pilot RCT, intensive and early basal insulin therapy versus standard care lowered PTDM risk at 12-months by 73%, possibly due to β-cell protection from stress hyperglycaemia [S56]. Larger studies are in progress to evaluate this further. Treatment of hepatitis C, a significant PTDM risk factor, with α-interferon prior to renal transplantation has shown reduced risk for PTDM [S57]. Choice of immunosuppressive regimen may also reduce risk of PTDM in high-risk individuals.

7. PTDM CONSIDERATIONS IN THE NON-RENAL SETTING (see Box 7)

Whilst most PTDM literature is in the setting of kidney transplantation, the burden of PTDM translates across other forms of SOT [S58]. General considerations are translatable across different solid organ settings. There are, however, some unique aspects to take into consideration with each specific organ.

PTDM after liver transplantation

Epidemiology and outcomes

Registry data suggest rates of PTDM after liver transplantation up to 40% [S59]. Non-alcoholic steatohepatitis (NASH) is a common cause of end-stage liver disease and transplant registry data confirms liver transplant recipients with NASH are more likely to develop PTDM. Hepatitis C, a common cause of end-stage liver disease, also increases risk for PTDM [S60]. A combination of these aetiological factors perhaps explains why incidence of PTDM is highest after liver transplantation. Registry data regarding outcomes are conflicting, although emerging data suggest increased mortality, and CVD associated with PTDM after liver transplantation [S59]. Weight gain is common following liver transplantation and should be mitigated. Treatment of hepatitis C virus may reduce the risk of PTDM [S57].

Liver transplant caveats for diagnosis and management

PTDM diagnostic classification should remain the same for liver transplant recipients, but there are specific considerations. Many liver transplant recipients will have renal impairment so the same precautions with HbA_{1c} still apply. In addition, interpretation of HbA_{1c} in the context of advanced liver disease may be difficult due to anaemia. Management of diabetes in the setting of liver impairment can be challenging as the liver is the major site of metabolism for many anti-diabetic medications, but metformin may be considered if liver allograft function is good and GFR permits.

PTDM after heart transplantation

Epidemiology and outcomes

Registry data report PTDM rates of 25-28% and 20% 5-years after heart transplantation [S61], with shared risk factors with other SOTs, but outcome data are limited. For example, diabetes is a known risk factor for death within a year of heart transplantation (hazard ratio 1.37, 95% CI 1.15-1.62) but this does not distinguish between pre-transplant and PTDM [S62].

Heart transplant caveats for diagnosis and management

Whilst there are no specific diagnostic considerations, PTDM management must consider sub-optimal heart allograft function. Thiazolidinediones and saxagliptin have a propensity to develop heart failure and should be avoided. The propensity for renal impairment and hyperkalaemia increases in the setting of heart failure and should lead to individualised pharmacological therapy for heart transplant recipients if there is sub-optimal heart allograft function.

PTDM after lung transplantation

Epidemiology and outcomes

A significant proportion of lung transplant recipients develop PTDM. In a prospective single-centre study using OGTT in 156 lung transplant recipients (25 with pre-existing diabetes), rates of PTDM after 3-months, 12-months and 24-months were 32%, 30% and 24% respectively in surviving patients [S63]. Registry data show PTDM incidence rates of approximately 30% and 40% among surviving lung transplant recipients by 5-years [S64]. The incidence of PTDM appears greater in people with cystic fibrosis, with half of patients having diabetes prior to lung transplantation and half of the remaining developing PTDM post-transplant [S65]. Outcome data are limited for lung transplant recipients who develop PTDM. A single-centre study from Melbourne analysing 210 lung transplant recipients demonstrated an increased risk of mortality with increasing degrees of hyperglycaemia but did not distinguish people with pre-transplant versus PTDM [S66].

Lung transplant caveats for diagnosis and management

No specific caveats exist in the diagnosis or management of PTDM in the setting of lung transplantation above and beyond those already discussed in other sections.

CONCLUSIONS

Observational studies involving hard outcomes of graft loss or mortality suggest that the diagnosis of PTDM is an important contributor to morbidity and mortality following SOT. The condition deserves careful monitoring and management, ideally by a multi-disciplinary team of specialists with combined expertise. This guideline has reviewed the current knowledge base and made evidence-based recommendations for the transplantation community.

The majority of studies in this area have been short-term, under-powered and used surrogate outcomes, and as a result large areas of uncertainty exist, and further research is warranted to develop evidence-based care for SOT recipients with, or at risk of, diabetes.

WORD COUNT: 5246

CONTRIBUTORSHIP:

Tahseen Chowdhury, Mona Wahba, Ritwika Mallik, Javeria Peracha and Adnan Sharif undertook the literature searches and first draft of the guidance. All other authors reviewed, re-reviewed and contributed to further revisions of the guidelines. TAC and AS are guarantors.

CONFLICTS OF INTEREST:

Tahseen A. Chowdhury - None

Mona Wahba - None

Ritwika Mallik – None

Javeria Peracha - None

Dipesh Patel - has received honoraria for advisory work and/or lecture fees from AstraZeneca, Boehinger Ingelheim Eli Lilly, MSD and Napp Pharmaceuticals, Novo Nordisk and Sanofi.

Parijat De – has received speaker honoraria from Novo Nordisk, Lilly, Sanofi, Napp, Boehringer-Ingelheim, Astra, Pfizer.

Damian Fogarty – declares speaker honoraria from Vifor, Napp & Pharmacosmos.

Andrew Frankel – declares receipt of research grants, preparation of educational materials and attendance at drug advisory boards for Astra-Zeneca, Boehringer Ingelheim/Lilly Alliance, Merck-Sharpe and Dohme, Napp Pharmaceuticals Ltd and Novo Nordisk.

Jannaka Karraliede - has received honoraria for delivering educational meetings and/or attending advisory boards Boehringer Ingelheim, Astra Zeneca, Sanofi, Janssen, Novo Nordisk. Research grants from: Astra Zeneca, Sanofi.

Patrick B. Mark - reports speaker honoraria from Vifor, Astrazeneca, Janssen, Napp, Novartis; research grants from Boehringer Ingelheim and non-financial support from Pharmacosmos.

Rosa M Montero – None.

Ana Pokrajac - non-promotional speaker fees, advisory boards and conference attendance by NAPP and NovoNordisk and Ellie Lily-BI Alliance.

Sagen Zac Varghese- None.

Stephen C. Bain – reports honoraria, teaching and research sponsorship/grants from AstraZeneca, Boehringer Ingelheim, Eli Lilly & Co, GlaxoSmithKline, Merck Sharp & Dohme, Novo Nordisk, Roche, Sanofi-Aventis, funding for development of educational programs from Cardiff University & Medscape. He owns a share of Glycosmedia and has provided expert advice to the All-Wales Medicines Strategy Group and National Institute for Health and Care Excellence (NICE) UK.

Indranil Dasgupta – None.

Debasish Banerjee – None.

Peter Winocour - has received honoraria for delivering educational meetings and/or attending advisory boards for Astra Zeneca, Boehringer Ingelheim, Eli Lilly, MSD, Napp, Sanofi, Novo and Vifor Pharmaceuticals.

Adnan Sharif – reports advisory boards for Boehringer Ingelheim, Eli Lilly, Sandoz, Astellas, Atara Biotherapeutics, Novartis, honoraria and grant funding from Chesi, Napp Pharamceuticals, Eli Lilly and travel reimbursement from Sandoz, Novartis.

Table 1. Current understanding or risk factors for PTDM

Non-modifiable	Modifiable

• Age
• Ethnicity
  – Black
  – Hispanic
  – South-Asian
• Family history of diabetes mellitus
• Cause of end-stage renal failure
  – Polycystic kidney disease
• Gender
• HLA mismatch
• Deceased-donor kidney
• Genetics
• Innate immunity
	• Previous stress related hyperglycaemia
	• Obesity
	• Metabolic syndrome
	• Pre-transplant triglycerides
	• Cytomegalovirus
	• Hepatitis C
	• Immunosuppression
	  – Tacrolimus
	  – Ciclosporin
	  – Sirolimus
	  – Corticosteroids
	  – Basiliximab
	• Rejection episodes
	• Anti-hypertensive medications
	  – Beta blockers
	  – Thiazide diuretics
	• Reduced glomerular filtration rate
	• Hypomagnesaemia

Table 2 . Glycaemic targets in people with diabetes and Diabetic Nephropathy-CKD

	Glycaemic target	**Note**
Type 1 diabetes	48–58 mmol/mol (6.5–7.5%)	Younger patients within 10 years' duration of diabetes and variable microalbuminuria–CKD stage 2
	58–62 mmol/mol (7.5–7.8%)	The majority of patients with proteinuria and/or CKD stages 3–4
	58–68 mmol/mol (7.5–8.5%)	Patients with CKD stage 5-dialysis
Type 2 diabetes	48–58 mmol/mol (6.5–7.5%)	For the majority of patients who are aged <40 years, or have CKD stages 1–2 (no basis to aim for <52 mmol/mol (6.9%) unless the patient is aged <40 years and has CKD stages 1–2)
	52–58 mmol/mol (6.9–7.5%)	For those with CKD stages 3–4 this target may be appropriate with a GLP-1–SGLT-2 inhibitor-based treatment regimen without insulin
	58–68 mmol/mol (7.5–8.5 %)	For those with CKD stages 3–4-proteinuria who are on an insulin-based regimen, and those with CKD stage 5 who are on dialysis

Table 3. Commonly used immunosuppressive drugs and their diabetogenic risk

Immunosuppressive drugs	**Post-transplant diabetes mellitus risk**
Corticosteroids	Increased
Tacrolimus	Increased
Ciclosporin	Slightly increased
mTORi	Slightly increased
Mycophenolate Mofetil	No effect
Azathioprine	No effect
Belatacept	Slightly decreased?
Basiliximab	Slightly increased?

REFERENCES

1. Byrne C, Caskey F, Castledine C, Davenport A, Dawnay A, Fraser S, Maxwell H, Medcalf JF, Wilkie M, Williams AJ. UK Renal Registry 20th Annual Report of the Renal Association *Nephron* 2018;139 (suppl 1).
2. Sharif A, Heckin M, de Vries APR et al. Proceedings from an international consensus meeting on posttransplant diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014;14:1992-2000.
3. Davidson J, Wilkinson A, Dantal J, Dotta F, Haller H, Hernandez D et al. New-onset diabetes after transplantation: 2003 International consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003;75(10 Suppl):SS3-24.
4. Arner P, Gunnarsson R, Blomdahl B, Groth CG. Some characteristics of steroid diabetes: a study in renal-transplant recipients receiving high-dose corticosteroid therapy. *Diabetes Care* 1983;6(1):23-5.
5. Sharif A, Shabir S, Chand S, Cockwell P, Ball S, Borrows R. Meta-analysis of calcineurin-inhibitor-sparing regimens in kidney transplantation. *J Am Soc Nephrol* 2011;22(11):2107-18.
6. McCaughan JA, Courtney AE. The clinical course of kidney transplant recipients after 20 years of graft function. *Am J Transplant* 2015;15(3):734-40.
7. Hagen M, Hagen M, Hjelmesæth J, Jenssen T, Mørkrid L, Hartmann A. A 6-year prospective study on new onset diabetes mellitus, insulin release and insulin sensitivity in renal transplant recipients. *Nephrol Dial Transplant* 2003;18(10):2154-9.
8. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003;3(2):178-85.
9. Dienemann T, Fujii N, Li Y, Govani S, Kosaraju N, Bloom RD, Feldman HI. Long-term patient survival and kidney allograft survival in post-transplant diabetes mellitus: a single-center retrospective study. *Transpl Int* 2016;29(9):1017-28.
10. Eide IA, Halde TAS, Hartmann A, Åsberg A, Dahle DO, Reisaeter AV, Jenssen T. Mortality risk in post-transplantation diabetes mellitus based on glucose and HbA1c diagnostic criteria. *Transpl Int* 2016;29(5):568-78.
11. Gaynor JJ, Ciancio G, Guerra G, Sageshima J, Hanson L, Roth D et al. Single-centre study of 628 adult, primary kidney transplant recipients showing no unfavourable effect of new-onset diabetes after transplant. *Diabetologia* 2015;58(2):334-45.
12. Eide IA, Halde TAS, Hartmann A, Åsberg A, Dahle DO, Reisaeter AV, Jenssen T. Associations Between Posttransplantation Diabetes Mellitus and Renal Graft Survival. *Transplantation* 2017;101(6):1282-1289.
13. Cole EH, Johnston O, Rose C, Gill J. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. *Clin J Am Soc Nephrol* 2008;3(3):814-21.

14. Kuo HT, Sampaio MS, Vincenti F, Bunnapradist S. Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. *Am J Kidney Dis* 2010;56(6):1127-39.
15. Valderhaug TG, Hjelmesæth J, Jenssen T, Røislien J, Leivestad T, Hartmann A. Early posttransplantation hyperglycemia in kidney transplant recipients is associated with overall long-term graft losses**.** *Transplantation* 2012;94(7):714-20
16. Johal S, Jackson-Spence F, Gillott H, Tahir S, Mytton J, Evison F,et al. Pre-existing diabetes is a risk factor for increased rates of cellular rejection after kidney transplantation: an observational cohort study. *Diabet Med* 2017;34(8):1067-1073.
17. Wauters RP, Cosion FG, Fernandez MLS, Kudva Y, Shah P, Torres VE. Cardiovascular consequences of new-onset hyperglycemia after kidney transplantation. *Transplantation* 2012;94(4):377-82.
18. Lentine KL, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol* 2005;16(2):496-506.
19. Porrini E, Díaz JM, Moreso F, Lauzurrica R, Ibernon M, Torres IS, Ruiz RB, Rodríguez AER, Mallén PM, Bayés-Genís B, Gainza FJ, Osorio JM, Osuna A, Domínguez R, Ruiz JC, Sosa AJ, Rinne AG, Miranda DM, Macías M, Torres A Prediabetes is a risk factor for cardiovascular disease following renal transplantation. *Kidney Int* 2019;96(6):1374-80.
20. Burroughs TE, Swindle J, Takemoto S, Lentine KL, Gerardo Machnicki G, Irish W et al. Diabetic complications associated with new-onset diabetes mellitus in renal transplant recipients. *Transplantation* 2007;83(8):1027-34.
21. Londero TM, Giaretta LS, Farenzena LP, Manfro RC, Canani LH et al. Microvascular Complications of Posttransplant Diabetes Mellitus in Kidney Transplant Recipients: A Longitudinal Study. *J Clin Endocrinol Metab* 2019;104(2):557-567.
22. Sundaram H, Smith RD, Viero R, First MR. Diabetic nephropathy after renal transplantation: Clinical and Pathologic Features. *Transplantation* 1996;62:632-5
23. Bhalla V, Nast CC, Stollenwerk N, Tran S, Barba L, Kamil ES, Danovitch G, Adler SG. Recurrent and de novo diabetic nephropathy in renal allografts. *Transplantation* 2003;75(1):66-71
24. Cheungpasitporn W, Thongprayoon C, Vijayvargiya P, Anthanont P, Erickson SB. The Risk for New-Onset Diabetes Mellitus after Kidney Transplantation in Patients with Autosomal Dominant Polycystic Kidney Disease: A Systematic Review and Meta-Analysis. *Can J Diabetes* 2016;40(6):521-528.
25. Ruderman I, Masterson R, Yates C, Gorelik A, Cohney SJ, Walker RG. New onset diabetes after kidney transplantation in autosomal dominant polycystic kidney disease: a retrospective cohort study. *Nephrology* (Carlton). 2012 Jan;17(1):89-96.

26. Heisel O, Heisel R, Balshaw R, Keown P. New onset diabetes mellitus in patients receiving calcineurin inhibitors: a systematic review and meta-analysis. *Am J Transplant* 2004;4(4):583-95.
27. Duijnhoven EM, Boots JM, Christiaans MH, Wolffenbuttel BH, Van Hooff JP. Influence of tacrolimus on glucose metabolism before and after renal transplantation: a prospective study. *J Am Soc Nephrol* 2001;12(3):583-8.
28. Tamura K, Fujimura T, Tsutsumi T, Nakamura K, Ogawa T, Atumaru C et al. Transcriptional inhibition of insulin by FK506 and possible involvement of FK506 binding protein-12 in pancreatic beta-cell. *Transplantation* 1995;59(11):1606-13.
29. Weir MR, Fink JC. Risk for posttransplant Diabetes mellitus with current immunosuppressive medications. *Am J Kidney Dis* 1999;34(1):1-13.
30. Porrini E, Delgado P, Alvarez A, Cobo M, Pérez L, González-Posada JM, Hortal L**,** Gallego R, García JJ, Checa M, Morales A, Salido E, Hernández E, Torres A. The combined effect of pre-transplant triglyceride levels and the type of calcineurin inhibitor in predicting the risk of new onset diabetes after renal transplantation. *Nephrol Dial Transplant* 2008;23(4):1436-41.
31. Triñanes J, Rodriguez-Rodriguez AE, Brito-Casillas Y, Wagner A, De Vries APJ, Cuesto G, Acebes A, Salido E, Torres A, Porrini R. Deciphering Tacrolimus-Induced Toxicity in Pancreatic β Cells. *Am J Transplant* 2017;17(11):2829-2840.
32. McCaughan JA, McKnight AJ, Maxwell AP. Genetics of new-onset diabetes after transplantation. *J Am Soc Nephrol* 2014;25(5):1037-49.
33. Valderhaug TG, Hjelmesæth J, Hartmann A, Røislien J, Bergrem HA, Leivestad T, Line PD, Jenssen T. The association of early post-transplant glucose levels with long-term mortality. *Diabetologia*. 2011;54(6): 1341–1349.
34. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 2006;29(5):1130-9.
35. Sharif A, Moore RH, Baboolal K. The use of oral glucose tolerance tests to risk stratify for new-onset diabetes after transplantation: An underdiagnosed phenomenon. *Transplantation* 2006;82(12):1667-72.
36. Valderhaug TG, Jenssen T, Hartmann A, Midtvedt K, Holdaas H, Reisaeter AV, et al. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. *Transplantation* 2009;88(3):429-34.
37. Mollar-Puchades MA, Malek-Marin T, Merino-Torres JF, Ramos-Escorihuela D, Sánchez-Plumed J, Piñón-Sellés F. Diabetes mellitus after kidney transplantation: role of the impaired fasting glucose in the outcome of kidney transplantation. *J Endocrinol Invest*, 2009;32(3):263-6.
38. International Expert Committee. International Expert Committee report on the role of the A_{1C} assay in the diagnosis of diabetes. *Diabetes Care* 2009;32(7):1327-34.

39. De Marchi S, Cecchin E, Basile A, Donadon W, Lippi U, Quaia P, Tesio F. More on the increase of hemoglobin A1 in chronic renal failure: the role of acidosis. *Nephron* 1983;35(1):49-53.
40. Coban E, Ozdogan M, Timuragaoglu A. Effect of iron deficiency anemia on the levels of hemoglobin A_{1c} in nondiabetic patients. *Acta Haematol* 2004;112(3):126-8.
41. Hoban R, Gielda B, Temkit MH, Saha C, Book BK, Baker E et al. Utility of HbA_{1c} in the detection of subclinical post renal transplant diabetes. *Transplantation* 2006;81(3):379-83.
42. Shabir S, Jham S, Harper L, Ball S, Borrows R, Sharif A. Validity of glycated haemoglobin to diagnose new onset diabetes after transplantation. *Transpl Int* 2013;26(3):315-21.
43. Yates CJ, Fourlanos S, Colman P, Cohney SJ. Screening for new-onset diabetes after kidney transplantation: limitations of fasting glucose and advantages of afternoon glucose and glycated hemoglobin. *Transplantation* 2013;96(8):726-31.
44. Eide IA, Halden TAS, Hartmann A, Åsberg A, Dahle DA, Reisæter AV, Jenssen T. Limitations of hemoglobin A1c for the diagnosis of posttransplant diabetes mellitus. *Transplantation* 2015;99(3):629-35.
45. Tillmann FP, Rump LC, Quack I. HbA1c levels at 90 days after renal transplantation in non-diabetic recipients predict de novo pre-diabetes and diabetes at 1 and 3 years after transplantation. *Int Urol Nephrol* 2018;50(8):1529-1534.
46. Werzowa J, Pacini G, Hecking M, Fidler C, Haidinger M, Brath H et al. Comparison of glycaemic control and variability in patients with type 2 diabetes and post-transplant diabetes mellitus after renal transplantation. *J Diab Comps* 2015;29:1211-6
47. Pasti K, Prokai A, Meszaros C, Peko N, Solyom R. et al. Continuous glucose monitoring system (CGMS) in kidney-transplanted children. *Pediatr Transplant* 2013;17(5):454-60.
48. Rodriguez LM, Knight RJ, Heptulla RA. Continuous glucose monitoring in subjects after simultaneous pancreas-kidney and kidney-alone transplantation. *Diabetes Technol Ther*, 2010;12(5):347-51.
49. Baker JR, O'Connor JP, Metcalf PA, Lawson MR, Johnsone RN. Clinical usefulness of estimation of serum fructosamine concentration as a screening test for diabetes mellitus. *BMJ* 1983;287(6396):863-7
50. Gupta S, Pollack T, Fulkerson C, Schmidt K, Oakes DJ, Molitch ME, Wallia A. Hyperglycemia in the Posttransplant Period: NODAT vs Posttransplant Diabetes Mellitus. *J Endocr Soc*. 2018;2(11):1314-1319. doi: 10.1210/js.2018-00227.