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

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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

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SUMMARY OF RECOMMENDATIONS

EPIDEMIOLOGY

1. Data relating to diagnosis of PTDM should be routinely collected for accurate auditing of incidence, prevalence and outcomes (Ungraded).

2. Micro- and macrovascular outcome data for solid organ transplant recipients with PTDM should be collected (Ungraded).

PATHOGENESIS

1. Counselling of risk for PTDM should consider individualised risk factors (Grade 1B).

DETECTION

1. Avoid diagnosis of PTDM in the immediate post-operative period when transient hyperglycaemia is extremely common (Grade 1B).

2. Afternoon capillary blood glucose monitoring (AGM) is recommended to identify patients with post-operative hyperglycaemia. These patients need close monitoring and formal testing for PTDM when clinically stable (Grade 1B).

3. A formal diagnosis of PTDM can be made from 6-weeks post-transplantation (Grade 1B).

4. Oral glucose tolerance test is the current gold standard for diagnosis of PTDM. While it may not be practical to use routinely in all solid organ transplant recipients prospectively, it should be utilised when possible for additional risk stratification and/or diagnostic clarification (Grade 1B).

5. HbA1c ≥6.5% (48mmol/L) is a suitable diagnostic test in clinically stable solid organ transplant recipients after the first 3 months post-transplantation (grade 1B).

6. Caution with the use of HbA1c must be exercised in the presence of factors that may impair accurate interpretation (Grade 1A).
7. In stable patients combining the results from abnormal fasting plasma glucose (FPG) ≥7mmol/L and/or HbA1c >6.5% (48mmol/mol) will detect the majority of PTDM cases (Grade 2C).

8. Patients awaiting transplant should receive annual glycaemic testing with FPG +/- HbA1c. High risk patients should then go on to have OGTT to confirm diagnosis of diabetes or screen for impaired glucose tolerance (Grade 2C).

9. The use of novel diagnostic tools such as fructosamine and glycated albumin are undetermined and cannot be recommended as clinical tools (Grade 2D)

MANAGEMENT

1. Immediately post-transplant, early post-operative hyperglycaemia (glucose >11 mmol/L on two occasions within 24 hours) should be actively monitored and treated. If hyperglycaemia is mild (<14.0 mmol/L), then oral hyperglycaemic therapy can be considered. Otherwise, early insulin therapy should be instituted either intravenously or subcutaneously (Grade 1C).

2. Glycaemic target for people with PTDM should be around 7% (53 mmol/mol), but adjusted according to degree of chronic kidney disease, age, co-morbidity, ability to self-manage, and patient preference (Grade 1B).

3. All people with a confirmed diagnosis of PTDM should be offered structured diabetes education (Grade 1B).

4. The diagnosis of PTDM must be conveyed to the patients’ usual primary care practitioner, and the patient should be put on to a diabetes register, and offered structured diabetes care, along with regular screening for complications (Grade 1B).

5. If patients with a stable eGFR ≥30 mls/min/1.73m² and BMI ≥25 kg/m², metformin should be considered first line oral therapy for people with confirmed PTDM (Grade 1C).

6. Other therapies which may be used safely in PTDM include sulfonylureas, meglitinides, DPP-4 inhibitors, pioglitazone and GLP-1 analogues. Use of
sulfonylureas and meglitinides should be undertaken with care especially in those at risk of hypoglycaemia (Grade 2C).

7. SGLT-2 inhibitors should be used with caution in patients with stable eGFR and poor glycaemic control, after careful discussion with nephrology and diabetes specialists (Grade 1C).

8. Insulin therapy should be considered in all patients who have inadequate glucose control, or who have symptomatic hyperglycaemia (Grade 1C).

9. Blood pressure should be controlled below 130/80 mmHg in all people with PTDM (Grade 1B).

10. All people with PTDM should be offered statin therapy, irrespective of cholesterol level (Grade 2D).

11. All people with PTDM should have access to specialist diabetes expertise within a multidisciplinary team setting (Grade 1C).

**MODIFICATION OF IMMUNOSUPPRESSION**

1. While immunosuppression is a major risk factor for PTDM, any planned modification to attenuate this risk should be balanced against the risk for allograft rejection (Grade 1B).

2. Individualisation of immunosuppression based on the recipient’s immunologic and glycaemic risk must be taken as part of an overall strategy to improve long term transplant outcome (Grade 1C).

3. Until further evidence emerges, we adopt the recommendation that the choice of immunosuppressive therapy should be primarily to prevent rejection rather than preventing PTDM (Grade 1C).

4. There is no evidence to suggest changing immunosuppressive therapy when hyperglycaemia is detected has a role in the management of PTDM (Grade 2B).

5. There is as yet no evidence that newer agents such as belatacept are beneficial in reducing risk of PTDM compared to tacrolimus-based regimens (Grade 1C).
**PREVENTION**

1. The risk for development of diabetes should be assessed as part of a pre-transplant work-up for all people being considered for transplantation (Grade 1B).

2. All people awaiting renal transplantation should be educated on the risk of developing PTDM, should be counselled about minimising weight gain using lifestyle measures, and should see a nutritionist with expertise in this area (Grade 1B).

3. Treatment of risk factors for PTDM such as hepatitis C should be considered in patients awaiting transplantation (Grade 1C).

4. In people considered at high risk for the development of PTDM, consideration should be given to immunosuppressive therapy that is less prone to inducing hyperglycaemia but this should be based on individualised risk with immunological status in mind (Grade 1C).

5. All patients deemed at high risk for development of PTDM should be screened yearly for diabetes whilst awaiting transplantation (Grade 1B).

**CONSIDERATIONS IN THE NON-RENAL SETTING**

1. Organ-specific factors should be considered when counselling patients for their risk of PTDM prior to solid organ transplantation (Grade 1B).

2. The diagnosis of PTDM should be consistent across different solid organ transplant settings, with organ-specific caveats in mind to determine the optimal diagnostic test (e.g. accuracy of HbA1c) (Grade 1C).

3. The management of PTDM should be consistent across different solid organ transplant settings, with organ-specific caveats in mind to determine the optimal management strategy (Grade 1B)
INTRODUCTION

Since the first successful renal transplant between identical twins in Boston in 1954, this modality of renal replacement therapy has improved the lives of millions of people with end stage renal disease (ESRD) worldwide. In the UK in 2017/8 there were 4,757 patients awaiting renal transplantation, and 3,272 renal transplants were undertaken [1]. The benefits of renal transplantation on morbidity and mortality in patients with chronic kidney disease (CKD) are well described. In the UK, the 10-year survival for recipients of living kidneys is 90%, whilst recipients of kidneys from deceased donation after brain or cardiac death have 10-year survival of 77% and 74% respectively [1]. By contrast, 10-year survival for patients on haemodialysis starting at the age of 55-64 years is significantly worse at around 30% [1]. Furthermore, solid organ transplantation for patients with end organ failure is a well-established and life-saving treatment.

Whilst diabetes mellitus is recognised as the most important cause of ESRD worldwide [2-4], in people who do not have diabetes undergoing transplantation, a high risk for the development of dysglycaemia has been recognised for over 40 years. Post-Transplant Diabetes Mellitus (PTDM), previously termed New Onset Diabetes after Transplantation (NODAT) was first recognised after liver transplantation by Starzl and colleagues in 1964 [5]. Since then, the condition has been extensively investigated and suggested to affect between 10% and 40% of patients undergoing solid organ transplantation. It is clear that hyperglycaemia post-transplant has a significant adverse impact on renal and other outcomes. As people live longer with transplants, cardiovascular morbidity and mortality becomes more prevalent, and PTDM appears to be an important risk factor for these complications.

PTDM results from similar risk factors to that of Type 2 diabetes (T2D), but in addition, specific transplant related factors have an important role. The aim of this guideline is to focus specifically on dysglycaemia or diabetes mellitus recognised primarily after transplantation. We recognise, however, that a number of people with PTDM may well have undetected pre-transplant diabetes mellitus. Indeed, the term NODAT was changed to PTDM by a Consensus report in 2014, to reflect the time of diagnosis rather than the time of onset [6]. As most data on PTDM exists in renal transplantation, we aim to focus on this area, but also include some data on other solid organ transplantation that may add to the
present evidence / knowledge base. While these recommendations focus on the topic of PTDM in non-diabetic solid organ transplant candidates and recipients, they are also of relevance for solid organ transplant recipients with pre-existing diabetes who are likely to suffer glycaemic deterioration post-transplantation.

We aim to review the definition of PTDM, and the evidence behind screening, diagnosis, hyperglycaemic and immunosuppressive management, and discuss potential methods for prevention of the condition. In each section, we aim to produce evidence graded recommendations, and areas for further research.
2.0 EPIDEMIOLOGY OF PTDM

2.1 Recommendations

1. Data relating to diagnosis of PTDM should be routinely collected for accurate auditing of incidence, prevalence and outcomes (Ungraded).
2. Micro- and macrovascular outcome data for solid organ transplant recipients with PTDM should be collected (Ungraded)

2.2 Areas for future research

1. Determine the incidence of PTDM longitudinally post-transplantation among different patient cohort groups.
2. How does the standardised incidence ratio differ for development of diabetes comparing a transplant versus general population cohort?
3. What are the long-term outcomes associated with PTDM across different population cohorts?
4. Does progression of micro- and macrovascular complications differ for patients with PTDM compared to other forms of diabetes mellitus?
5. Do micro- and macrovascular outcomes differ for patients with PTDM compared to other forms of diabetes mellitus?
6. Is the epidemiology of PTDM changing in the contemporary climate of solid organ transplantation?

2.3 Audit recommendations

1. What proportion of PTDM patients are recorded correctly in hospital and primary care records?
2. What proportion of patients with PTDM have regular screening for microvascular complications of diabetes?
2.4 Overview

Understanding the epidemiology of PTDM has been complicated by the lack of clear diagnostic criteria, with harmonisation of diabetes classification with the general population only occurring with the original Consensus guidelines published in 2003 [1]. While this aided understanding in both the incidence and prevalence of PTDM, we still lack a clear understanding of long-term outcomes related to PTDM. The study of PTDM has primarily been conducted in the setting of kidney transplantation, but some of the risk factors for development of PTDM will be shared with other solid organ transplant setting and will be discussed further in Section 8.

2.5 Incidence and prevalence of PTDM

Prior to 2003, the 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 incidence and prevalence rates reported by different centres were not comparable to other units. In the era of glucocorticoids and azathioprine, the incidence of diabetes was reported in up to 50% of recipients [2], but introduction of calcineurin inhibitors (CNIs) (first ciclosporin and then tacrolimus), with a shift to more steroid-sparing exposure, reported rates of PTDM declined but were still incredibly variable between 2% to 53% due to the lack of uniform diagnostic practice [3]. This prompted the 2003 Consensus meeting to formulate guidelines to achieve a standard of care for diagnosis, prevention and management of PTDM [1].

Utilising contemporary diagnostic criteria for PTDM in the publication of the original Consensus guidelines, a clearer picture of the scale of dysglycaemia after solid organ transplantation is being ascertained. However, even in studies using the current consensus criteria, the reported incidence of PTDM can still vary between 9% and 39% in the first-year post-transplantation [4], and likely reflects distinct patient demographics and immunosuppression practice. Beyond the first year after transplantation, it is difficult to determine whether the incremental risk of developing PTDM is over and above the risk compared to the general population. However, with increasing longevity of both transplant recipients and their allograft, the presumption is the cumulative exposure to diabetogenic risk factors (both traditional and transplants-specific) leads to increased risk for PTDM. For
example, the incidence of de novo PTDM after 20 years of kidney graft survival is reportedly low at only 8% in a Northern Irish cohort (n=706) transplanted between 1968 and 1993 [5]. The diagnostic criteria for PTDM was, however, the need for oral hypoglycaemic or insulin therapy, and therefore is likely to significantly under-estimate the true incidence of long-term PTDM.

One controversial issue is whether the incidence of PTDM is declining. There are many putative explanations for this; increased awareness, rationalised immunosuppression, reduced rejection rates. For example, contemporary immunosuppression regimens across the majority of transplant centres adopt CNI-sparing regimens (to avoid the risk of associated nephrotoxicity) and such strategies to reduce exposure to tacrolimus or ciclosporin are associated with significantly reduced odds of developing PTDM [6]. In a Norwegian single-centre analysis of patients undergoing oral glucose tolerance testing (OGTT) at 10-weeks post-transplant, the odds of developing PTDM appear to have halved between 1997 and 2007 [7]. While abnormal glucose metabolism developing beyond 10 weeks may have been undetected, repeat testing of this cohort at 6 years found an increase in kidney transplant recipients with a normal oral glucose tolerance test (OGTT) from 46% to 65% [8]. Data from the United States Annual Data Report also documents a fall in the incidence of PTDM at 1-, 3- and 5-years after kidney transplantation over the last decade, though it is unclear if the same definition of diabetes was maintained throughout (17). Work from Porrini and colleagues, has demonstrated a bimodal distribution to the incidence of PTDM and implies a cumulative increase in long-term risk for surviving transplant recipients [9].

One of the reasons for a lack of clarity in the data relates to the absence of inclusion of PTDM as part of routine returns to transplant registries. Such additional information will facilitate a greater understanding of the long-term impact of PTDM, which currently is limited to published literature from single-centre studies rather than a population-cohort study using robust diagnostic criteria.

### 2.6 Impact of PTDM on long-term mortality

PTDM has shown to be associated with increased risk for mortality after transplantation, although there is some inconsistency in the literature with regards to long-term mortality.
The majority of studies report PTDM to be independently associated with increased risk for mortality after kidney transplantation [10-15], but other studies have reported no association between PTDM and patient survival [16, 17]. There are, however, limitations to many of these studies that skew our interpretation of the long-term impact of PTDM. For example, some studies have only found an association between PTDM and mortality if individuals were taking glucose-lowering therapy [10]. Eide and colleagues only observed a mortality risk for kidney transplant recipients with PTDM based on glucose-based diagnostic criteria rather than the use of glycated haemoglobin for diagnosis [11]. Studies showing no association between PTDM and mortality may be limited by short duration of follow up. For example, Gaynor and colleagues who demonstrated no link between new-onset diagnosis of PTDM with risk for mortality had follow up to 56-months only [16]. Kuo and colleagues also demonstrated no link between PTDM and mortality but had follow up to 36-months [17]. The lack of robust data collection by national transplant registries for PTDM is a major limiting factor to accurately assess the impact of PTDM on mortality and needs rectifying.

2.7 Impact of PTDM on long-term graft loss

The association between PTDM and graft loss is less clear. While an association with overall graft loss is well recognised (driven by mortality), the association between PTDM and death-censored graft loss is more ambivalent [12]. Cole and colleagues, in their analysis of the United States Renal Data System (USRDS) registry, observed a similar impact of PTDM and acute rejection on risk for overall graft loss due to different mechanisms; PTDM was associated with increased risk for mortality but not death-censored graft loss while rejection had a contrasting effect [15]. The worst overall outcome existed for patients who developed both rejection and PTDM, similar to finding from Matas and colleagues [18]. Valderhaug and colleagues also observed an association between PTDM (based upon 2-hour postprandial glucose) and overall graft loss but not death-censored graft loss [19].

2.8 Impact of PTDM on morbidity and quality of life

Rejection remains the leading cause of patient concern [20] but the relationship between PTDM and rejection is not bi-directional. Treatment for allograft rejection includes large corticosteroid boluses, which is consistently shown to be a risk factor for PTDM, but it is unclear if PTDM leads to an increased risk for rejection. While pre-existing diabetes at the
time of kidney transplantation has been associated with increased risk for rejection after kidney transplantation [21], the data linking PTDM with increased subsequent risk for rejection is scarce.

Numerous publications have shown an association between PTDM and increased risk for cardiovascular events [22-24], which likely is the leading contributor to the observed increase in mortality rates. Review articles of cardiovascular disease after kidney transplantation consistently cite PTDM as a risk factor worthy of detection, prevention and management [25]. While it appears risk for cardiovascular events from PTDM may not be as high as pre-existing diabetes, this likely reflects the difference in cumulative exposure to glycaemia, or the presence of pre-existing metabolic syndrome, rather than PTDM having different prognostic implications for cardiovascular events.

Data in relation to microvascular complications are limited for PTDM. Burroughs and colleagues observed the emergence of diabetes-related microvascular complication after new-onset PTDM occurred in over half of kidney transplant recipients within three years of follow up [26]. Median time to onset of microvascular complications was approximately 1.8 years, contrasting sharply with the general population [26]. However, this contrasts with recent data from Londero and colleagues who analysed 64 kidney transplant recipients with PTDM of at least 5-years duration (mean duration of 8-years) [27]. They observed a lower than expected prevalence of microvascular complications, with no evidence of any diabetic retinopathy but more evidence of neuropathy (e.g. distal symmetric polyneuropathy) [27].

There is no published work exploring quality of life for solid organ transplant recipients who develop PTDM. Qualitative work from kidney transplant recipients in Australia cites development of diabetes after transplantation as a leading concern [20], but no work has explored quality of life parameters for patients with versus without PTDM. The need for diabetes therapies, plus additional monitoring is likely, however, to have an adverse effect on quality of life.
3.0 PATHOGENESIS OF PTDM

3.1 Recommendations

1. Counselling of risk for PTDM should consider individualised risk factors (Grade 1B)

3.2 Areas for future research

1. Clarify risk factors for development of PTDM in context of uncertain or conflicting published literature (e.g. risk for PTDM with polycystic kidney disease)
2. Does the pathophysiology of early onset PTDM differ from late-onset PTDM?
3. What contribution do individual risk factors make as part of the combined risk for PTDM?
4. Is a stratified approach to high-risk patients for diagnosis, prevention and/or management effective to prevent PTDM?
5. How can the pre-transplant genetic risk for PTDM be utilised in a clinical application to reduce risk?

3.3 Audit recommendations

1. What proportion of patients are informed of their risk for developing PTDM whilst awaiting transplantation?
3.4 Overview

PTDM must be considered as a distinct metabolic entity from other forms of diabetes and its pathogenesis reflects this separation. This is an important distinction as an increased understanding of the drivers for the development of PTDM could lead to more targeted intervention for prevention and management. While solid organ transplant recipients have the same generic risk factors for diabetes as the general population, their additional exposure to unique transplant-specific risk factors is the key factor that leads to the significant burden of PTDM.

3.5 Risk factors for PTDM

Risk factors for the development of PTDM are well documented, with numerous review articles on the topic [1,2]. Briefly, risk factors can be categorised as non-modifiable versus modifiable, or generic versus transplant-specific, and are summarised in Table 1 below:

Table 1. Current understanding or risk factors for PTDM

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>• Previous stress related diabetes or hyperglycaemia</td>
</tr>
<tr>
<td>• Ethnicity</td>
<td>• Obesity</td>
</tr>
<tr>
<td>– Black</td>
<td>• Metabolic syndrome</td>
</tr>
<tr>
<td>– Hispanic</td>
<td>• Pre-transplant triglycerides</td>
</tr>
<tr>
<td>– South-Asian</td>
<td>• Cytomegalovirus</td>
</tr>
<tr>
<td>• Family history of diabetes mellitus</td>
<td>• Hepatitis C</td>
</tr>
<tr>
<td>• Cause of end-stage renal failure</td>
<td>• Immunosuppression</td>
</tr>
<tr>
<td>– Polycystic kidney disease</td>
<td>– Tacrolimus</td>
</tr>
<tr>
<td>• Gender</td>
<td>– Ciclosporin</td>
</tr>
<tr>
<td>• HLA mismatch</td>
<td>– Sirolimus</td>
</tr>
<tr>
<td>• Deceased-donor kidney</td>
<td>– Corticosteroids</td>
</tr>
<tr>
<td>• Genetics</td>
<td>– Basiliximab</td>
</tr>
<tr>
<td>• Innate immunity</td>
<td>• Rejection episodes</td>
</tr>
<tr>
<td></td>
<td>• Anti-hypertensive medications</td>
</tr>
</tbody>
</table>
While some risk factors are well acknowledged (e.g. age, ethnicity, immunosuppression), others are more speculative with conflicting evidence base. For example, the data is conflicting with regards to whether adult polycystic kidney disease (APKD) is a risk factor for PTDM or not with published studies showing either a positive [3,4] or negative [5-7] association. A recent meta-analysis of all published cohort studies did suggest that the pooled empirical data demonstrates an association between APKD and risk for PTDM [8]. However, heterogenous study cohorts with poorly defined PTDM means the data may not translate across all populations.

Understanding the underlying risk profile can help risk stratify, and to appropriately counsel kidney transplant recipients of their risk for developing PTDM, facilitating additional support or pre-emptive modifications to peri- and/or post-transplant management to attenuate the risk for developing PTDM. However, such pro-active approaches need to be tailored to the individual and be based on evidence.

3.6 Pathophysiology of PTDM

Underlying risk factors have an important role in the development of PTDM and partially explain our increasing understanding of the pathophysiology of PTDM, which supports its distinction as a separate metabolic entity from other forms of diabetes.

3.6.1 General pathophysiology of diabetes mellitus

Type 1 Diabetes (T1D) is well recognised to be an autoimmune disorder characterised by the destruction of insulin-producing pancreatic β-cells, whilst T2D is characterised by a combination of declining insulin secretion in the presence of insulin resistance [9]. Variation
in beta-cell insulin secretion, as a response to the state of insulin resistance, is controlled by changes in the secretory capacity of the beta-cell and not as a direct influence of glucose [10]. This hyperbolic relationship also implies the existence of a feedback loop mechanism: for glucose metabolism to remain constant the beta cell has to have the ability to make proportionate and reciprocal alterations to insulin secretion in the context of variable insulin sensitivity. Further work is required to determine the mechanism of this feedback loop, but it appears that glucose may not be alone in mediating this regulation [11]. Abnormalities of the beta cell occur before the onset of hyperglycaemia. Beta cell dysfunction begins as a response to the state of insulin resistance, with a compensatory increase in insulin secretion to maintain the physiological constant to control glucose metabolism. Further decline in insulin sensitivity leads to further compensatory measures by the beta cell to maintain this hyperbolic relationship. Throughout this period of physiological flux between insulin secretion and sensitivity, a state of normoglycaemia exists. The inability of the beta cell to secrete an adequate quantity of insulin in the state of insulin resistance heralds the onset of hyperglycaemia and failure to attenuate this subsequently leads to the onset of T2D.

3.6.2 Pathophysiology of diabetes in setting of uraemia and/or liver dysfunction

Insulin secretion is not affected in uraemic subjects [12]. Rather, the uraemic state is associated with insulin resistance as a result of tissue insensitivity to the metabolic actions of insulin [40]. The primary site of insulin resistance resides in the peripheral tissue as opposed to either augmented hepatic glucose production or impaired hepatic glucose uptake [13].

Renal gluconeogenesis, and the dual contributions of the renal cortex and medulla to glucose homeostasis, is important in the pathophysiology of diabetes mellitus. It is speculated that 20-25% of glucose released into the circulation in the fasting state originates from the kidneys through gluconeogenesis [14]. Evidence to support a skewed balance of glucose utilisation versus release in the context of renal failure can be extrapolated from the observation that exogenous insulin requirements decrease in patients who develop end-stage renal failure [15]. One of the explanations for this phenomenon is the prolonged biological half-life of insulin due to a loss of renal insulin excretion [16]. However, the observation of hypoglycaemia in non-diabetic renal failure patients raises the possibility of decreased renal gluconeogenesis, secondary to a loss of renal cortex tissue, as an additional
contributory factor [17]. This is supported by the findings suggesting the kidney plays an important role in glucose counter-regulation [18].

The concept of hepatogenous diabetes, defined as a state of impaired glucose regulation caused by loss of liver function due to cirrhosis, has long been recognised. Both beta-cell dysfunction and insulin resistance are believed to contribute to its pathophysiology, with the latter believed to be the predominant defect [19]. However, many of these defects likely occur pre-cirrhotic stages and evidence suggests diabetes rates increase with worsening stages of cirrhosis [20], although this finding is not consistent [21]. Combined with underlying aetiology of liver disease, with some causes of liver dysfunction associated with an increased risk for diabetes, the complex interplay between liver dysfunction and diabetes risk becomes an important yet poorly understood issue in the context of PTDM.

### 3.6.3 Pathophysiology of PTDM

The development of PTDM occurs in the context of declining insulin secretion in the presence of insulin resistance [22], which at first glance appears similar to T2D [23]. Many generic and transplantation-specific risk factors are been associated with the development of PTDM, as discussed above, which contribute to the underlying pathophysiology. However, a number of areas remain poorly understood with regards to the pathophysiology of PTDM in comparison to other forms of diabetes.

Hagen and colleagues conducted a 6-year prospective study assessing the change in glucose metabolism in renal transplant recipients [24]. They found a decline in insulin secretion was the dominant mechanism by which PTDM developed. They also documented that an improvement in insulin sensitivity could normalise glucose intolerance, and this fits in with the hyperbolic relationship previously discussed and the concept of the disposition index.

The role of calcineurin inhibitors in the pathogenesis of PTDM is well documented, with tacrolimus having a stronger association than ciclosporin for the condition [25-27]. Duijnhoven et al. [28] examined the impact of tacrolimus on glucose metabolism prospectively using a frequently sampled, intravenous glucose tolerance test. Tacrolimus commencement was associated with a significant decrease in the insulin sensitivity index as a result of diminished insulin secretion (there was no associated change in insulin
resistance). Patients with abnormal insulin sensitivity indexes in this study appeared to be at greater risk of developing PTDM on longitudinal follow up. Tacrolimus trough level reduction from 9.5 to 6.4 ng/ml was shown to improve pancreatic beta-cell secretion as assessed by C-peptide secretion (49.0 to 66.6 nmol.min/l, p = 0.04), although there was a borderline statistical significance for insulin secretion (1134 to 1403 mU.min/l, p = 0.06). It therefore appears likely the diabetogenicity of calcineurin inhibitors is dose-dependent and the clinical challenge is to achieve a balance between attainment of efficacy and minimisation of side effects.

Calcineurin inhibitors (CNIs) like tacrolimus and ciclosporin are associated with the up-regulation of insulin gene expression, decreasing insulin synthesis by transcriptional inhibition of insulin mRNA [29]. In vitro and in vivo studies have shown CNIs may also affect insulin secretion, in addition to inhibition of insulin synthesis, through reversible toxicity to the pancreatic beta cell [30]. Hirano et al. [31] demonstrated the reversible toxicity of tacrolimus on rat islets; high dose treatment was associated with functional (impaired insulin secretion and reduced pancreatic insulin levels) and structural (vacuolation of the islets on histopathological examination) changes, which reversed by two weeks after cessation of the drug. In addition, CNIs have also been suggested to have an influence on insulin sensitivity [29].

The role of glucocorticoids in development of PTDM also warrants mention. Glucocorticoids interfere with carbohydrate metabolism and insulin secretion and action via a number of mechanisms, including inducing insulin resistance by effects on insulin receptors in liver, muscle and adipose tissue.

While agreement exists that PTDM involves a combination of increased insulin resistance and beta-cell dysfunction, the relative importance of each component remains debated. To the extent that insulin resistance may not manifest as hyperglycaemia after transplantation until pancreatic beta-cells are unable to compensate, beta-cell dysfunction is probably necessary for overt PTDM. No significant research has investigated changes in glucagon, incretin hormones or renal handling of glucose post-transplantation, although limited experience exploiting renal handling of glucose suggests a possible route of pharmacological intervention even in a transplant setting.
3.6.4 Unique aspects of PTDM pathophysiology

Elucidating the primary pathophysiological defect in PTDM is important as it may help prioritise a rational hierarchy of therapeutic intervention (such as choosing insulin secretagogues versus sensitisers). However, it is more likely that pathophysiological mechanism(s) for the development of PTDM, and the relative contribution of various mechanistic components, will be heterogenous across different patient characteristics and time period post transplantation. A feature unique to PTDM is the magnitude of dynamic change in glucose metabolism state, especially within the first few months post-transplant with the majority undergoing rapid reduction in overall immunosuppression burden or conversely a minority who require additional corticosteroids for acute rejection. Hyperglycaemia consistent with a diagnosis of diabetes is ubiquitous among renal transplant recipients within the first weeks post-transplant and there is evidence that hyperglycemia requiring inpatient insulin therapy that improves is still associated with 4-fold increased risk for subsequent development of PTDM [30,31]. This bi-directional nature of glucose metabolism in the setting of solid organ transplantation is unique and clinically well demonstrated [21, 32].

Finally, PTDM is distinguished by the interplay of an unusually large number of generic and transplant-specific variables. In addition, genetic polymorphisms are an important risk factor for PTDM and recent work from genome-wide association studies supports the hypothesis that pancreatic beta-cell dysfunction is critical in the development of PTDM, with a number of single-nucleotide polymorphisms identified in genes that are associated with beta-cell apoptosis [33]. However, insulin resistance remains important and the metabolic syndrome (putatively with insulin resistance as the key pathophysiological defect) is prevalent after transplantation [34]. Current consensus is that pancreatic beta-cell dysfunction is the predominant pathophysiological defect in early onset PTDM, with insulin resistance the major contributor to late onset PTDM and prospective cohort studies will be important to distinguish both pathophysiological and clinical features of different forms of PTDM.
4.0 DETECTION OF PTDM

4.1 Recommendations

1. Avoid diagnosis of PTDM in the immediate post-operative period when transient hyperglycaemia is extremely common (Grade 1B).
2. Afternoon capillary blood glucose monitoring (AGM) is recommended to identify patients with post-operative hyperglycaemia. These patients need close monitoring and formal testing for PTDM when clinically stable (Grade 1B).
3. A formal diagnosis of PTDM can be made from 6-weeks post-transplantation (Grade 1B).
4. Oral glucose tolerance test is the current gold standard for diagnosis of PTDM. While it may not be practical to use routinely in all solid organ transplant recipients prospectively, it should be utilised when possible for additional risk stratification and/or diagnostic clarification (Grade 1B).
5. HbA1c ≥6.5% (48mmol/L) is a suitable diagnostic test in clinically stable solid organ transplant recipients after the first 3 months post-transplantation (grade 1B).
6. Caution with the use of HbA1c must be exercised in the presence of factors that may impair accurate interpretation (Grade 1A).
7. In stable patients combining the results from abnormal fasting plasma glucose (FPG) ≥7mmol/L and/or HbA1c >6.5% (48mmol/mol) will detect the majority of PTDM cases (Grade 2C).
8. Patients awaiting transplant should receive annual glycaemic testing with FPG +/- HbA1c. High risk patients should then go on to have OGTT to confirm diagnosis of diabetes or screen for impaired glucose tolerance (Grade 2C).
9. The use of novel diagnostic tools such as fructosamine and glycated albumin are undetermined and cannot be recommended as clinical tools (Grade 2D)

4.2 Areas for future research

1. Does method of PTDM detection impact upon long-term outcomes?
2. Do solid organ transplant recipients with transient hyperglycaemia post-transplant have an increased risk for future PTDM?
3. What are the long-term outcomes for solid organ transplant recipients with impaired fasting glucose, impaired glucose tolerance or pre-diabetes?

4. Does risk of PTDM differ for recipients with impaired fasting glucose versus impaired glucose tolerance?

5. Are there any additional benefits from fructosamine and/or glycated albumin as diagnostic tools for PTDM?

4.3 Audit recommendations

1. Is there a formal protocol for screening for pre-existing diabetes in people awaiting transplantation?

2. What proportion of patients screened for hyperglycaemia in the immediate post-transplant period?

3. What proportion of patients following transplantation undergo yearly HbA1c screening?

4. What proportion of patients with normal or abnormal HbA1c have anaemia?
4.4 Overview

The current guidelines recommend the use of the term PTDM and not to use the term new-onset diabetes after transplantation (NODAT) anymore, since this term implies that diabetes prior to transplantation has been adequately excluded which is often not the case, and may be impractical for many transplant programs. NODAT also inadequately describes allograft recipients who develop diabetes post-transplantation after an earlier transient hyperglycaemic period that has resolved.

There has been no clear definition of the criteria for PTDM diagnosis until the publication of the first PTDM consensus guidelines in 2003 [1]. This lack of uniform diagnostic criteria explains the heterogeneity in reported rates for PTDM incidence after kidney transplantation, ranging from as low as 3% to greater than 40% in the published literature [2,3]. Several older publications have used discharge with prescription of glucose-lowering therapies as the sole definition of PTDM, which leads to an underestimation of the true incidence of PTDM in historical publications. Therefore, the first consensus guideline from 2003 proposed to adopt the diabetes mellitus definition endorsed by the American Diabetes Association (ADA) at that time. Since the ADA guidelines for the diagnosis of diabetes mellitus have been subsequently revised, the most recent consensus guidelines for PTDM have taken these changes into account such as inclusion of HbA1c as diagnostic tool for PTDM [4]. Also, in parallel to ADA recommendations, the current PTDM guidelines emphasise the clinical relevance of pre-diabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]), since both conditions are likely to confer increased risks for the development of PTDM, and IGT per se has been suggested as an independently predictor of mortality [5,6].

A further important issue that required resolution was the time-point after which PTDM should be officially diagnosed. The development of significant hyperglycaemia is ubiquitous among non-diabetic kidney transplant recipients in the immediate early post-operative phase [7,8]. Although early post-operative hyperglycaemia may be a risk-factor for subsequent development of PTDM, it should not be used as diagnostic criterion for PTDM since many cases are transient. This fact has been considered in the current guidelines which recommend that PTDM diagnosis should only be made in the later stable clinical period beyond the first 6-weeks after transplantation [4]. After this initial hyperglycaemic peak
during the first few weeks after transplantation, the incidence of PTDM increases with time after transplantation [9] and has been shown to have a bimodal incidence risk [10].

4.5 Fasting plasma glucose (FPG)

A fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) is one criterion for the diagnosis of diabetes mellitus and fasting is defined as absence of caloric intake for at least 8 hours [11]. Impaired fasting glucose (a pre-diabetic state) is defined by the ADA as FPG between 5.6 mmol/L (100 mg/dL) and 6.9 mmol/L (125 mg/dL), and the World Health Organisation (WHO) as 6.1 mmol/L (110 mg/dl) to 6.9 mmol/L. Determination of FPG is a relatively easy and quick screening method for glucose homeostasis alterations but has several important limitations.

Isolated elevation of FPG is a consequence of hepatic insulin resistance with normal muscle insulin sensitivity and often is combined with defects in the early-phase insulin secretory response [12]. In non-transplanted subjects, IFG is much more common in men than in women and there is relatively little overlap with IGT [13]. In stable kidney transplant recipients, without a history of diabetes or pre-diabetes, the prevalence of isolated IFG has been reported to be between 12-18 %, isolated IGT was found in approximately 9% and combined IFG/IGT in between 12-14% [14,15]. In the general population, sole determination of FPG would miss approximately one third of patients with diabetes who have an isolated defect in glucose tolerance [16]. In kidney transplant recipients, the situation is similar: 25-30% of patients with PTDM would be missed based solely upon isolated determination of PTDM using FPG [14,17]. Maintained FPG in the normal range despite impaired glucose tolerance is also pathophysiologically linked to renal disease since reduced renal clearance of insulin predisposes for low FPG and elevated postprandial glycaemia [18].

Some transplant centres have utilised a hybrid approach and combined diagnostic tools by facilitating an oral glucose tolerance test (OGTT) stratified by a threshold fasting glucose level. In one study, OGTTs were performed in almost 1500 kidney transplant recipients, with specificity and sensitivity of FPG for the diagnosis of PTDM analysed [17]. The authors found an “optimal” threshold for performing an OGTT at a FPG value of 5.3 mmol/L (96 mg/dL). Using a lower FPG threshold of 5.0 mmol/l (90 mg/dL) would still not detect all PTDM patients (91%) but nearly two-thirds of patients would have to undergo an OGTT. These data
also indicate that approximately 10% of patients with FPG of 5.0 mmol/L (90 mg/dL) and below may still be diagnosed with PTDM on the basis of an OGTT. These data were confirmed by a study by Bergrem and colleagues, which found only 20% of all kidney transplant recipients with PTDM would have been diagnosed based upon FPG glucose alone [19]. The authors of this study recommend an even lower FPG threshold for the performance of OGTT; in their cohort a FPG threshold of 5.1 mmol/L (92 mg/dL) would identify 90% PTDM patients and require undertaking an OGTT in 50% of all patients at risk. There is no clear recommendation for the performance of OGTT in patients with a FPG ≥7.0 mmol/L (126 mg/dL) since this finding alone suffices for the diagnosis of PTDM. As holds true for many laboratory tests – pathologic glucose measurements should be repeated and no treatment decisions should be based on a single measurement [20].

During the first 4-6 weeks after transplantation, especially in centres using high corticosteroid doses usually administered in the morning, FPG alone is of even lower value in detecting hyperglycaemia since these patients typically experience hyperglycaemic peaks in the afternoon [7,21]. Despite these limitations of FPG, it is acknowledged that patients with high values have poorer outcomes regarding graft and patient survival [22], and it remains a simple and generally effective screening test.

4.6 2-h plasma glucose during oral glucose tolerance testing

Performance of an OGTT (75 g of anhydrous glucose dissolved in water) is now widely accepted as the gold standard for diagnosis of PTDM and remains the diagnostic test of choice in the recent consensus guidelines due to a number of factors [4]. As previously highlighted, an OGTT will detect more patients with PTDM than measurement of FPG alone. In addition, it offers the possibility of detecting IGT, a pre-diabetes condition defined by a 2-h plasma glucose (2hPG) between 7.8-11.0 mmol/L (140-199 mg/dL). IGT is pathophysiologically distinct from IFG and potentially has different therapeutic, as well as prognostic, implications in the general population as well as post-transplantation [64, 68, 69]. It is characterised by peripheral (muscle) insulin resistance and defects in early- and late-phase insulin response. In kidney transplant recipients the presence of IGT has been identified as an independent predictor of mortality, with each 1 mmol/L increment in 2hPG leading to a 5% increase in risk of all-cause mortality and a 6% increase in risk of cardiovascular-related mortality [6]. However, IGT has been shown to be positively
influenced by life-style interventions in the general population and IFG appears to be less likely improved by such interventions [23,24]. Similar positive effects of life-style and pharmacological interventions on IGT have also been shown in kidney transplant recipients [25,26].

The disadvantages of OGTT include poor reproducibility and a relatively high time expenditure which makes its routine application for every kidney transplant unrealistic. The logistical obstacles for large and expanding prevalent solid organ transplant cohorts under secondary care follow up to prospectively use routine OGTTs for diagnostic purposes is challenging. The advantages of an OGTT should be reserved for specific situations, possibly stratified by other screening mechanisms such as combined risk factors or threshold FPG levels, to identify at-risk solid organ transplant recipients where diagnostic clarification of PTDM is essential.

4.7 Glycated haemoglobin (HbA1c)

For the diagnosis of diabetes, measurement of HbA1c has a number of advantages compared to fasting plasma glucose and 2hPG. These advantages include; standardised methods for quantification, better index of overall glycaemic exposure, less biologic variability, less pre-analytic instability, no need for fasting or timed samples, widely accepted use and minimal influence due to acute perturbations in glucose levels [27]. These advantages led to the decision to adopt HbA1c as diagnostic marker for diabetes mellitus by the ADA and WHO in 2009 [11]. The utility of HbA1c in the diagnosis of PTDM has been matter of debate, with the majority of published literature focused on kidney transplant recipients. HbA1c is formed by a non-enzymatic posttranslational glycation in a two-step reaction via an aldimine to form the ketoamine HbA1c in the presence of glucose [28]. The rate of glycation depends on temperature, pH, haemoglobin concentration, concentration of glucose and duration of glucose exposure. In patients with impaired kidney function the elevated urea levels lead to the generation of cyanate leading to the formation of carbamylated haemoglobin [29]. High levels of carbamylated haemoglobin interfere with the measurement of HbA1c leading to falsely high HbA1c levels only when charge-dependent HbA1c assays are used, but not with standardised HPLC-based methods. Other factors that can lead to falsely elevated HbA1c levels are acidosis [30], and iron deficiency [31]. There are also several factors that can artificially decrease HbA1c levels, including blood loss, blood cell
transfusions, shortened erythrocyte survival time and erythropoietin treatment [32] - factors that commonly occur in patients after kidney transplantation. During the first year after kidney transplantation approximately 50% of patients may still be anaemic [33], potentially leading to falsely lowered HbA1c levels.

Prospective long-term data using HbA1c as diagnostic tool for PTDM with analysis of macro- and microvascular complications are lacking, but there are several smaller studies explore the accuracy of HbA1c testing after kidney transplantation. Hoban and colleagues analysed 199 kidney transplant recipients, comparing FPG levels and HbA1c, and demonstrated 14/20 patients with an elevated HbA1c had FPG in the normal range [34]. HbA1c may therefore be more sensitive than FPG, especially in African Americans, although no OGTTs were performed in this study to verify the diagnosis of PTDM. In a study by Shabir and colleagues, HbA1c levels were compared in non-diabetic kidney transplant recipients with OGTT results at 3- and 12-months after transplantation [35]. The study demonstrated an HbA1c value ≥6.5% was associated with an 88.9% concordance for a positive OGTT-derived PTDM diagnosis at 3- and 12-months after transplantation. Conversely, a normal OGTT had a 98.7% concordance for an HbA1c <6.5%. A further study tried to determine the optimal HbA1c level at which an OGTT should be performed in order to detect PTDM [17]. The authors found that an HbA1c cut-off value of 5.8% has a sensitivity of 83% for the detection of PTDM and would help to avoid the performance of an OGTT in every transplant recipient. However, HbA1c testing seems to be of little value in the early postoperative phase (0-3 months), because HbA1c levels tend to be falsely lowered and only OGTT or afternoon glucose measurements should be performed for the detection of PTDM [36]. However, HbA1c has been shown to be very predictive of risk of pre-diabetes and PTDM at 1- and 3-years after kidney transplantation in a single-centre study [37], although in a recent meta-analysis of six studies (n=2,057 kidney transplant recipients), early use of HbA1c was shown to be highly specific but low/moderately sensitive to diagnose PTDM [38]. While supporting the use of alternative diagnostic tools in the early period after transplantation, certainly at 1-year after kidney transplantation a combination of FPG and HbA1c has been shown to be as good as an OGTT to capture persistent PTDM [39].

Taken together, it would appear HbA1c measurements can be used in stable kidney transplant recipients for the detection of transplant associated hyperglycaemia and PTDM but not during the first three months after transplantation. While certain caveats in
comparison to OGTT exist, its ease of use from a logistical perspective makes it an attractive diagnostic tool for detection of PTDM.

4.8 Continuous glucose monitoring (CGM)

CGM devices have now become widely available and its use has brought (limited) improvements in the management of type 1 diabetes (T1D) for distinct groups of patients, especially in combination with continuous subcutaneous insulin infusions (CSII), and for hypoglycaemia unawareness [40]. Besides these clinical advantages, CGM offers the unique possibility to obtain continuous glucose profiles over days and weeks enabling clinicians to calculate glycaemic indices that could otherwise not be obtained [41]. These indices can help to describe glycaemic variability and control – parameters that are crucial for the pathophysiological understanding of diabetes mellitus and its treatment and may even help to predict the risk of diabetes-related complications [42].

Since kidney transplant recipients represent a group of patients with distinct alterations in glucose metabolism, for the most part due to the influences of immunosuppressive therapy, CGM technology holds promise in helping to gain a deeper understanding of PTDM. For example, it has been recently observed using CGM monitoring that patients with type 2 diabetes mellitus show a higher glycaemic variability than patients with PTDM [43]. Yates and colleagues have demonstrated, using CGM monitoring that divided dosing of prednisone reduced glycaemic variability in kidney transplant recipients [44]. Two studies, one in children and one in adults, described the usefulness of CGM in kidney transplant recipients to detect hyperglycaemic episodes that would have remained undetected by routine laboratory testing [45,46]. Wojtusciszyn and colleagues showed in non-diabetic patients immediately after kidney transplantation that mean glucose levels determined by CGM are elevated in nearly every patient and that the degree of hyperglycaemia in this early phase might help identify patients at risk for later development of PTDM and graft failure [47]. CGM is therefore highly useful in the detection of early postoperative hyperglycaemia because FPG is often normal in these patients, HbA1c is not reliable during the first three months after transplantation and OGTT is impractical in post-operative patients on the ward.
4.9 Fructosamine and glycated albumin

Fructosamine and glycated albumin are alternative measures for chronic glycaemia but their linkage to average glucose and their prognostic significance are less clear when compared to HbA1c and therefore there is no recommendation for their use in clinical practice guidelines for diabetes mellitus. Glucose binds to serum proteins in a non-enzymatic reaction in proportion to its serum concentration by a process called glycation leading to the generation of glycated proteins. The term fructosamine refers to the sum of all ketoamine linkages between circulating glucose and serum proteins. These compounds do not contain fructose as the name is suggesting, but the resulting chemical product resembles the open-chain form of fructose (this implies that ALL glycated proteins in the blood are fructosamines) [48]. Therefore, the main portion of fructosamine in the blood is glycated albumin since this is the most abundant serum protein. The half-life of serum albumin is 2-3 weeks and fructosamine therefore correlates with glycaemic control during the previous 1-3 weeks and can be seen as medium-term marker for glycemia [49]. Determination of fructosamine as an index of diabetic control was introduced in the early 1980s [50], but has so far shown little benefit in the care of diabetes patients over blood glucose and HbA1c monitoring [51]. Thus, fructosamine is usually only used in situations when no reliable HbA1c measurements are possible, such as in patients with haemoglobinopathies or anaemia.

Considering the limitations of HbA1c as a diagnostic tool in selected solid organ transplant recipients, there could be some rationale to determination of fructosamine or glycated albumin but this remains under research. There are only few publications on fructosamine or glycated albumin in the context of renal impairment for example. Morgan and colleagues found a good correlation between HbA1c and mean blood glucose in patients on haemodialysis but the correlation between fructosamine and mean glucose was poor, probably due the shortened half-life of albumin in haemodialysis patients [52]. Another study compared the levels of fructosamine in healthy individuals to non-diabetic patients with chronic kidney disease (CKD), patients on haemodialysis, patients on peritoneal dialysis and finally patients after kidney transplantation; only kidney transplant recipients showed fructosamine levels similar to healthy controls [53]. One study found better correlations of glycated albumin and fructosamine with mean serum glucose as determined by CGM in CKD patients stage 4 and 5 (including dialysis patients) as compared to HbA1c [54], while another demonstrated glycated albumin as a better indicator of glycaemia then HbA1c in
haemodialysis patients receiving erythropoietin therapy due to the above mentioned influences erythropoietin on HbA1c levels [55]. However, many laboratories do not offer assays for glycated albumin and in light of the paucity of data and their contradictory results, the use of glycated albumin and fructosamine cannot be recommended for the diagnosis of PTDM at present. Larger studies evaluating their use in kidney transplant recipients would definitely be necessary to clarify this issue.
5.0 MANAGEMENT OF PTDM

5.1 Recommendations

12. Immediately post-transplant, early post-operative hyperglycaemia (glucose >11 mmol/L on two occasions within 24 hours) should be actively monitored and treated. If hyperglycaemia is mild (<14.0 mmol/L), then oral hyperglycaemic therapy can be considered. Otherwise, early insulin therapy should be instituted either intravenously or subcutaneously (Grade 1C).

13. Glycaemic target for people with PTDM should be around 7% (53 mmol/mol), but adjusted according to degree of chronic kidney disease, age, co-morbidity, ability to self-manage, and patient preference (Grade 1B).

14. All people with a confirmed diagnosis of PTDM should be offered structured diabetes education (Grade 1B).

15. The diagnosis of PTDM must be conveyed to the patients’ usual primary care practitioner, and the patient should be put on to a diabetes register, and offered structured diabetes care, along with regular screening for complications (Grade 1B).

16. If patients with a stable eGFR >30 mls/min/1.73m² and BMI >25 kg/m², metformin should be considered first line oral therapy for people with confirmed PTDM (Grade 1C).

17. Other therapies which may be used safely in PTDM include sulfonylureas, meglitinides, DPP-4 inhibitors, pioglitazone and GLP-1 analogues. Use of sulfonylureas and meglitinides should be undertaken with care especially in those at risk of hypoglycaemia (Grade 2C).

18. SGLT-2 inhibitors should be used with caution in patients with stable eGFR and poor glycaemic control, after careful discussion with nephrology and diabetes specialists (Grade 1C).

19. Insulin therapy should be considered in all patients who have inadequate glucose control, or who have symptomatic hyperglycaemia (Grade 1C).

20. Blood pressure should be controlled below 130/80 mmHg in all people with PTDM (Grade 1B).

21. All people with PTDM should be offered statin therapy, irrespective of cholesterol level (Grade 2D).
22. All people with PTDM should have access to specialist diabetes expertise within a multidisciplinary team setting (Grade 1C).

5.2 Areas for Future Research

1. What is the optimum management for in-patient hyperglycaemia in patients undergoing renal transplantation?
2. Is there a benefit of tight versus standard glucose control?
3. Are low carbohydrate diets effective for management of PTDM?
4. What is the role of SGLT-2 inhibitors and GLP-1 analogues in the management of PTDM?
5. Does choice of immunosuppressive regimen influence onset and management of PTDM?

5.3 Audit recommendations

1. What proportion of patients with PTDM have good glycaemic control as determined by their individualised glycaemic target?
2. What proportion of patients with PTDM and stable eGFR above 30 mls/min/1.73m$^2$ are treated with metformin?
3. What proportion of patients with a diagnosis of PTDM are offered structured diabetes education, and have regular foot and eye screening?
5.4 Overview

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 [1]. 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).

5.5 Early post-operative hyperglycaemia and glucose management in hospital

Dysglycaemia in the early post-operative period following renal transplantation is common, and may be due to post-operative stress hyperglycaemia, high doses of corticosteroids used for immunosuppression, pain, infection or indeed previously undiagnosed diabetes exacerbated by the above [1]. In addition, $\beta$-cell function and insulin secretion appears to drop significantly post-transplant possibly related to immunosuppression [2].

The prevalence of dysglycaemia appears to be very high. In one study of 424 patients undergoing renal transplantation, 87% of patients not known to have diabetes prior to transplantation developed hyperglycaemia [3]. One Chinese study of liver transplant recipients showed a prevalence of new onset hyperglycaemia of 42.6% in 3339 patients undergoing liver transplantation [4]. In a further study using continuous glucose monitoring sensors in 43 non-diabetic renal transplant recipients, hyperglycaemia was seen in all patients on day 1 post-transplant and in 43% of patients between day 1 and day 4 [5]. In-patient hyperglycaemia appears to be a good predictor of subsequent development of longer term PTDM. In a cohort of 377 patients undergoing renal transplantation, 30% of the cohort required hyperglycaemia treatment with insulin, and had a four-fold increased risk of PTDM compared to patients who did not require insulin [6]. Further studies have shown that in-patient hyperglycaemia is a potent risk factor for subsequent development of PTDM [7]. Early hyperglycaemia immediately post-operatively may also be a marker for acute rejection episodes [8] or chronic rejection [9], and peri-operative hyperglycaemia has been suggested as being associated with delayed graft function [10]. Day 1 post-operative hyperglycaemia has been suggested as a risk factor for increased risk of graft failure [11], although not in all
studies [12]. Post-operative stress hyperglycaemia is also noted to be a risk factor for mortality post liver transplantation [13].

Early post-operative insulin therapy following renal transplantation may have a role in preventing the subsequent development of PTDM. In a one-year proof of concept study, 50 renal transplant recipients were randomly assigned to immediate post-operative isophane insulin if evening glucose was > 140mg/dl (7.8 mmol/L) compared to standard treatment of short acting or oral hypoglycaemic therapy if evening glucose was 180-250mg/dl (10-14 mmol/L) [14]. Early isophane therapy appeared to lead to a 73% risk reduction in the subsequent development of PTDM. The early isophane therapy group appeared to have better β-cell function at one year, suggesting that the isophane therapy may have offered some β-cell protection. The same group subsequently used continuous subcutaneous infusion of insulin (CSII) immediately post-operatively in 24 patients without diabetes, and found better glucose control than with isophane although subsequent outcomes for PTDM have yet to be reported [15]. Tight glycaemic control has been shown to reduce risk of post-operative infection in patients with liver transplantation [16].

Early post-operative hyperglycaemia post transplantation shares some similarities with steroid-induced diabetes. Corticosteroids typically induce hyperglycaemia by increasing resistance to insulin [17], and whilst the initial dose of steroids is high in the early post-transplant period, it is usually rapidly titrated downwards. Nevertheless, early post-operative hyperglycaemia post transplantation can have a significant steroid component. The Joint British Societies Guidelines on the Management of Hyperglycaemia and Steroid Therapy [18], offer consensus-based guidelines on glucose management in this scenario. They suggest the use of short-acting sulfonylurea may be considered, titrated to a maximum dose of 240mg in the morning and 80mg in the evening. If this is unsuccessful then treatment with a morning dose of isophane insulin is advocated.

Hyperglycaemia in the early post-operative period requires careful monitoring and management. Hyperglycaemic emergencies immediately following transplantation have been reported, and exclusion of diabetic ketoacidosis or hyperosmolar hyperglycaemic syndrome is important in such patients. A retrospective study of 39,628 renal transplant recipients and found that the incidence of DKA was 33.2/1,000 individuals per year among
renal transplant recipients with DM and 1.9/1,000 individuals per year among recipients without DM [19].

Severe hyperglycaemia should be managed actively with variable rate intravenous insulin infusion, intravenous fluids and hourly blood glucose monitoring [20]. Specific glucose targets are not clear, but, as with many in-patient settings such as myocardial infarction or intensive care [21,22], there is no evidence for benefits of very tight glucose control in the in-patient post-transplant setting. Indeed one study suggests that a tight blood glucose target (70-100 mg/dl [3.9-5.5 mmol/L]) was associated with increased hypoglycaemia and future rejection episodes compared to a standard glucose target (70-180 mg/dl [3.9-10 mmol/L]) [23].

Once nutritional status is improved and the patient is stabilised, the patient should be converted from intravenous to subcutaneous insulin doses. There is strong evidence for one insulin regimen over another, and hence conversion to a once daily isophane insulin regimen (preferably given in the morning), with additional prandial insulin as needed, seems the most logical regimen to use.

5.6 Glycaemic targets in PTDM

Following the early post-operative period, the diagnosis of PTDM needs to be established (see section 2.0). Once established, the condition requires active monitoring and treatment.

There are a number of reports that suggest that PTDM has an adverse impact on patient survival, with some suggestion of a two-fold increase in mortality compared to people with normal glucose tolerance [24]. This increase in mortality largely attributable to increased cardiovascular mortality, although PTDM is also associated with increased risk of sepsis, [25], and CMV infection [26]. Similarly, many studies suggest a reduction in graft survival [24-27], although a potential source of bias is that rejection may lead to increased immunosuppression, and hence hyperglycaemia, rather than hyperglycaemia causing graft failure. A large retrospective study of people with PTDM has shown frequent microvascular complications of diabetes [28], suggesting that glucose control may be important in this respect. A more recent small Brazilian study, however, suggested that microvascular
complications were infrequent in PTDM [29]. Diabetic nephropathy has been described in subjects with PTDM [30].

Observational data suggests that glucose control may be important in patients with PTDM. In a Korean study of 3,538 kidney transplant recipients, 476 patients received kidney transplantation because of diabetic nephropathy [31]. Patients with diabetic nephropathy had poor graft and patient survival rates compared with non-diabetic nephropathy, and those patients with the highest quartile of time-averaged glucose had the worst graft outcomes. A study from Austria of 798 patients with renal transplants suggested that maximal glucose levels, but not HbA1c was associated with poorer mortality in renal transplant recipients [32]. A retrospective study from the US, however, showed no benefit of improved glucose control on renal outcomes 12 months post renal transplant [33]. In a study of 210 lung transplant recipients, however, each 1% rise in HbA1c was associated with a 48% increased risk of mortality [34].

There is currently no randomised trial evidence to suggest that better glucose control improves outcomes in people with post-transplant diabetes. In the absence of such evidence, guidelines for targets used in Type 2 diabetes are probably appropriate for patients with PTDM, with the caveat that a number of therapies have not been tested in PTDM. In the UK, NICE suggests an overall glucose target of around 7.0% (53 mmol/mol), but individualising glucose targets according to the persons’ co-morbidity and risk of hypoglycaemia [35]. NICE states that clinicians should “adopt an individualised approach……. taking into account personal preferences, co-morbidities, risks from polypharmacy, and ability to benefit from long term interventions because of reduced life expectancy”. They suggest that consideration should be given to “relaxing the target HbA1c on a case by case basis, with particular consideration for people who are older or frail….., who are unlikely to achieve longer term risk reduction benefits, and for whom intensive management would not be appropriate, for example, people with significant co-morbidities”.

More recent guidance from the American Diabetes Association (ADA) suggests an overall glucose target of 7.0% (53 mmol/mol), but similarly suggest that less stringent targets may be appropriate “for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes in whom the goal is difficult to achieve despite diabetes self-
management education, appropriate glucose monitoring, and effective doses of multiple glucose-lowering agents including insulin” [36].

KDIGO recommends a glycaemic target of 7-7.5% (53-58 mmol/mol) due to high risk of hypoglycaemia and frequent history of cardiovascular disease in patients undergoing renal transplantation [37]. The ABCD-RA guidelines on managing hyperglycaemia in patients with diabetes and diabetic nephropathy-chronic kidney disease suggest less stringent targets according to grade of CKD, which we feel should also apply to PTDM [38] (table 1).

Table 1 Glycaemic targets in patients with diabetes and DN-CKD

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

As the therapeutic armamentarium for management of hyperglycaemia increases, a number of newer therapies are now available to manage glucose in PTDM. This section aims to review the evidence behind each therapy and offer recommendations for their use.

One consideration when prescribing anti-diabetic therapy to patients with PTDM is the potential for interactions between immunosuppressants and anti-diabetic agents, which is well reviewed by Vanhove and colleagues [39]. For example cyclosporine inhibits cytochrome P450 3A4 enzyme, and may increases levels of prandial glucose regulators, gliptins, sulfonylureas and possibly sodium-glucose transporter-2 (SGLT-2) inhibitors. Although calcineurin inhibitors (CNIs) and mammalian target of rapamycin inhibitors (mTORi) are frequently prone to drug interactions, only glibenclamide and canagliflozin are likely to influence their levels significantly.

5.7.1 Diet and lifestyle-based management

Weight gain following transplantation is common. The reasons for this may be multifactorial, and probably include being allowed a less restrictive diet after transplantation, improved appetite off dialysis, corticosteroid use and inadequate lifestyle changes [40]. There is some suggestion that females are at higher risk of weight gain than males post-transplant [41]. Mean weight gain in some studies is around 4-8 kg [42, 43]. Dietary intervention may reduce weight gain post-transplantation, but it has been suggested that nutritional care for patients undergoing renal transplantation is frequently neglected [44]. In one study of 33 patients randomised to intensive versus standard dietary intervention, weight gain in the intensive group was limited to 5.5 kg, whilst the standard group gained 11.8 kg [45].

Higher weight pre-transplantation is a risk factor for the development of PTDM, and is a target for prevention (see later) [46]. A clinical trial of dietitian delivered active versus passive lifestyle intervention in 130 renal transplant recipients has been recently reported [47]. This has shown a reduction in development of PTDM, but the difference did not reach significance (7.6% versus 15.6% respectively, p=0.123). There was, however, a reduction in fat mass (mean difference -1.537kg [-2.947 to -0.127], p=0.033) and weight (mean difference
Further trials of use of high protein and low glycaemic index diets [48], and other dietary interventions are ongoing [49]. A recently published prospective study of 468 renal transplant recipients showed that a Mediterranean Style Diet was associated with a lower post-transplant diabetes risk [50].

In patients at risk for the development of diabetes, lifestyle intervention is proven to be of benefit for the prevention of diabetes [51,52]. There is currently no strong evidence that diet or lifestyle based will prevent or improve PTDM. Nevertheless, as diet and lifestyle change are the cornerstones of diabetes therapy in the non-transplant setting, high priority should be given to dietary intervention to manage hyperglycaemia and minimise weight gain in patients with PTDM.

5.7.2 Oral hypoglycaemics

5.7.2.1 Metformin

Metformin is contra-indicated in severe CKD with eGFRs below 30 mls/min/1.73m². In the post-transplant setting, however, there is an opportunity to consider using metformin in patients with pre-transplant diabetes and PTDM if renal function allows. Metformin, however, does not appear to be widely used. In a large US survey of 14144 renal transplant recipients with pre-transplant diabetes, only 4.7% of them received metformin in the first 12 months post-transplant. Subjects on metformin had a significantly lower all cause, malignancy related and infection related mortality [53]. In a further US based observational study of 46914 transplant recipients, just under 10% of these patients received metformin, and unsurprisingly they had low creatinine values, but also better transplant survival and lower mortality [54]. One small retrospective study had shown no significant adverse effects with an average of 16 months of metformin therapy post renal transplant [55]. Metformin has been recommended by some as a potential first line agent for the treatment of hyperglycaemia in PTDM, due to its low cost, efficacy, and potential anti-obesity, anti-inflammatory and anti-neoplastic effects [56].

Metformin is first line therapy for treatment of Type 2 diabetes in many international guidelines. Whilst there is no strong evidence for its use in the post-transplant setting, in
patients with stable renal function and no other contraindications, metformin therapy should be encouraged particularly in overweight patients with PTDM. The ABCD/RA guidance on managing hyperglycaemia in diabetes CKD suggest the use of metformin “sick day rules” whereby metformin therapy should be temporarily stopped if a person becomes acutely unwell, but restarted if possible on recovery [57].

5.7.2.2 Sulfonylureas / Meglitinides

Due to their rapid efficacy and ease of administration, sulfonylureas are used commonly in patients with PTDM, although there is no available safety data for their use [58]. Nevertheless, they may be useful in the early post-transplant period for mitigating the hyperglycaemia induced by corticosteroids (see above).

In a small observational study of 23 patients with post-transplant diabetes, repaglinide, a short acting prandial glucose regulator, was used to treatment hyperglycaemia. Mean HbA1c dropped from 7.6% to 5.8% in 14 patients, whilst the remaining nine subjects required progression to insulin therapy [59].

Whilst sulfonylureas and prandial glucose regulators may be useful in the early post-transplant period, their use must be balanced with the risk of hypoglycaemia, particularly when immunosuppressive regimes are being titrated downwards. Patients should be carefully counselled about this risk, and should undertake regular self-monitoring of glucose (SMBG).

5.7.2.3 Glitazones

Glitazones are safe and effective in patients with renal disease, and have been used in small studies of patients with PTDM. In one study of 10 patients treated with insulin or glyburide post-transplant, the addition of pioglitazone lowered HbA1c by around 1.4% (12 mmol/mol) and reduced dose of insulin [60]. A study of non-diabetic renal transplant recipients randomised to pioglitazone or placebo showed a modest benefit in carotid intima-media thickening [61]. Small studies of rosiglitazone (no longer available in Europe) have also been published, suggesting moderate efficacy [62,63]. In one study of 40 patients with PTDM
initially stabilised with insulin, all were converted to rosiglitazone at 3-4 months post-
transplant and only three out of 40 required insulin subsequently [64]. Glitazones may be
useful to treat liver steatosis in post liver transplant patients [65]. Adverse effects of fluid
retention, weight gain and increased fracture risk limit the use of these drugs in patients
with T2D, especially amongst those with renal disease.

5.7.2.4 Dipeptidylpeptidase-4 (DPP-4) inhibitors

By virtue of their lack of side effects and ease of administration, gliptins are now widely used
for the management of Type 2 diabetes. In animal models of PTDM, gliptins appear to have
beneficial effects on sirolimus induced oxidative stress [66]. There are some studies of their
use in the setting of PTDM, but all are small, short term and non-controlled. In a
retrospective study of 22 patients with PTDM treated with sitagliptin, 17 patients achieved
good glycaemic control (HbA1c <7.0%) [67]. In a prospective randomised cross over study of
19 patients with PTDM, sitagliptin 50-100mg was crossed over with a sitagliptin free period
of four weeks [68]. Sitagliptin improved first and second phase insulin responses, fasting and
post-prandial glucose levels.

Sitagliptin has also been used in a single centre pilot study of 15 patients with PTDM, and
found an HbA1c reduction of 0.5%, and no effect on sirolimus or tacrolimus levels [69]. A
further retrospective study from India of 21 patients with PTDM treated with linagliptin
found a decrease in HbA1c by an average of 0.6% (6mmol/mol) over 24 weeks treatment
[70]. A randomised trial of 32 patients with PTDM treated with vildagliptin or placebo
showed a significant reduction in 2-hour plasma glucose and HbA1c (by 0.4% {4 mmol/mol})
[71]. In a Korean study of 65 renal allograft patients with PTDM, comparison of the efficacy
of linagliptin, sitagliptin and vildagliptin was undertaken, and showed that linagliptin appears
to be more efficacious in reducing HbA1c compared to other gliptins (mean reduction of
1.4% (12 mmol/mol) in linagliptin treated patients) [72]. When compared to the addition of
insulin glargine to 17 patients with PTDM, the addition of sitagliptin to 28 patients
inadequately controlled PTDM led to similar reductions in HbA1c (0.6% {5 mmol/mol}), but
with a 1.2 kg difference in weight change between the two agents [73].

A recently published study of 14 patients treated with linagliptin plus insulin versus insulin
treated alone patients with post-transplant hyperglycaemia suggested that glucose control
was better and insulin dose and hypoglycaemia was lower in the linagliptin plus insulin treated group [74].

Vildagliptin has also been used in cardiac transplantation. In a study of 30 cardiac transplant patients with PTDM, 15 of who were treated with vildagliptin, and 15 of whom were not, showed a reduction in HbA1c of 0.6% (5 mmol/mol) [75]. Vildagliptin has also been used in post-transplant impaired glucose tolerance (IGT) [76]. In this study of 48 patients were randomised to pioglitazone, vildagliptin or placebo for three months. Two-hour plasma glucose fell in both groups significantly compared to placebo.

A systematic review and meta-analysis of five studies of gliptins in patients with PTDM suggested these drugs were effective in the post-transplant setting, leading to an average HbA1c reduction of 0.993% (10 mmol/mol), with no change in eGFR or Tacrolimus levels [77].

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

GLP-1 analogues are increasingly used in patients with CKD, with a number of agents licenced for use down to eGFRs of 15 ml/min/1.73m² [78]. They have the advantage of improving glucose control, with the addition of weight loss, which is useful in the post-transplant setting as outlined previously, as weight gain in common in this circumstance. There is very little data about the use of GLP-1 in the post-transplant setting, but small case series do suggest they may be effective. PTDM is characterized by reduced glucose-induced insulin secretion and reduced glucagon suppression during hyperglycaemic clamp, and studies of patients with PTDM using a GLP-1 infusion appears to improve these insulin and glucagon defects [79]. A case series of liraglutide used in five patients with PTDM resulted in significant reductions in fasting and two hour glucose levels and body weight, and did not result in changes in tacrolimus levels [80]. A further small retrospective case series of seven Taiwanese transplant patients saw a 1.9% (20 mmol/mol) reduction in HbA1c and 2.9 kg weight loss over a mean of 19.4 months of follow up [81].

The largest cohort of GLP-1 analogues in PTDM so far reported is a single centre retrospective chart review of 63 patients with solid organ transplants treated with the GLP-1 analogue, dulaglutide [82]. 49 patients had at least 12 months follow up, and mean weight
reduction of 4kg was seen, with HbA1c reduction of 0.4% (4 mmol/mol), and insulin dose reduction of a mean of around six units.

5.7.2.6 Sodium Glucose Transporter-2 (SGLT-2) inhibitors

There is increasing evidence that SGLT-2 inhibitors are cardio- and renoprotective [83]. Empagliflozin and canagliflozin have shown impressive benefits in patients with CKD, in particular in reducing progression to ESRD, doubling of serum creatinine and renal mortality. In the setting of PTDM, the potential side effect of genito-urinary infection is a concern [84,85], and rarely diabetic ketoacidosis may complicate therapy with these drugs [86]. Currently only two studies has reported on the use of SGLT-2 inhibitors in renal transplantation [87]. In this study, 14 patients with PTDM treated with insulin were converted to oral empagliflozin 10mg daily, of whom, two dropped out due to inadequate glucose control, two developed urinary tract infection, and two dropped out due to worsening renal function. Of the eight remaining patients, three required reinstitution of insulin therapy, and the other five remained stable on empagliflozin.

In a larger placebo controlled study of 44 renal transplant recipients, a very modest reduction in HbA1c of 0.2% (2 mmol/mol) was seen, although this was significantly greater than placebo [88]. Body weight reduced by a mean of 2.5 kg. The magnitude of HbA1c reduction was, however, dependent on baseline HbA1c and eGFR. There were no significant differences in adverse events.

A recent pilot study of canagliflozin in 24 renal transplant patients in India showed a mean 0.9% reduction in HbA1c in patients treated with the drug, along with a mean 25kg weight loss, with no significant adverse effects or change in serum creatinine [89].

5.7.2.7 Insulin

Insulin therapy is frequently required in PTDM, particularly in the early post-transplant period where acute hyperglycaemia following surgery, exacerbated by high dose immunosuppression and potentially infection. Once transplant function is more stable, however, and immunosuppression is reduced, there may be an opportunity to reduce or even stop insulin therapy.
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 patients, particularly as it may usefully reduce post prandial hyperglycaemia which is typical of steroid induced hyperglycaemia. As steroid doses are weaned, insulin doses may be able to be titrated downwards. Longer term, however, insulin therapy may be required in PTDM, and standard regimens such as basal insulin, twice daily fixed mixtures or basal bolus regimens may be required.

5.8 Management of cardiovascular risk factors in people with PTDM

Despite screening for cardiovascular disease in all patients prior to transplantation, cardiovascular disease is a significant problem amongst patients undergoing solid organ transplantation [90]. The addition of PTDM appears to add significantly to this burden of cardiovascular disease, and therefore cardiovascular risk reduction is mandatory. Traditional cardiovascular risk factors are not very predictive of cardiac events in renal allograft recipients [91].

Smoking cessation is mandatory, as there is a high risk of allograft failure in smokers compared to non-smokers [92], and smoking may increase the risk of diabetes post-transplant [93].

Dyslipidaemia is common amongst patients undergoing transplantation, which may be related to immunosuppression and other factors [94]. The Assessment of LEscol in Renal Transplantation (ALERT) study randomised over 2100 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 [95]. 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). Nevertheless, KDIGO guidelines suggest statin therapy for all renal transplant recipients [37], aiming for a target LDL cholesterol below 100mg/dl (2.59 mmol/L). There is little data on the use of non-statin medications in the post-transplant setting.
Hypertension is common post transplantation, and if uncontrolled, is associated with adverse graft outcomes. Angiotensin converting enzyme inhibition or angiotensin receptor blockade may be drugs of first choice in patients with stable renal function, but there is no strong evidence for benefit in graft survival or reduction in mortality [96]. Additionally, there is currently no strong evidence for the optimum blood pressure target for renal transplant recipients. The KDIGO guidelines suggest a target blood pressure of 130/80 mmHg for patients with renal allografts [37]. This concords with the blood pressure target of 130/80 mmHg in patients with diabetic renal disease and hypertension [96].

5.9 Structured diabetes care and screening for diabetes complications

All patients with diabetes should undergo annual checks for diabetes related complications in a structured way. In the UK, many patients with diabetes do not undergo their eight key processes of care (eye check, foot check, HbA1c, cholesterol, creatinine, albumin creatinine ratio, body mass index, smoking status) each year, and this may be exacerbated in patients with PTDM, in whom the responsibility for delivering these key processes may not be clear, particularly as many of these patients are attending specialist transplant clinics on a frequent basis. There is conflicting data about microvascular complications of diabetes in PTDM. One survey of 21,489 US renal data system patients with renal transplants suggested a lower rate of microvascular complications compared to patients with Type 2 diabetes, but in those who did develop complications, their progression appeared to be accelerated [29]. Therefore microvascular complications need careful and regular surveillance.

Therefore, all patients with PTDM should be registered in a primary care diabetes register, and receive standard call and recall for screening and management within primary care. Close liaison with the transplant team, however, will be required, especially when additional therapy for glucose or cardiovascular risk factors is warranted.

In large transplant centres, there may be a benefit in having all patients with post-transplant diabetes managed in a multi-disciplinary clinic involving diabetes and renal specialist nurses, doctors, pharmacists and dietitians.
6.0 MODIFICATION OF IMMUNOSUPPRESSION TO PREVENT OR TREAT PTDM

6.1 Recommendations

1. While immunosuppression is a major risk factor for PTDM, any planned modification to attenuate this risk should be balanced against the risk for allograft rejection (Grade 1B).

2. Individualisation of immunosuppression based on the recipient’s immunologic and glycaemic risk must be taken as part of an overall strategy to improve long term transplant outcome (Grade 1C).

3. Until further evidence emerges, we adopt the recommendation that the choice of immunosuppressive therapy should be primarily to prevent rejection rather than preventing PTDM (Grade 1C).

4. There is no evidence to suggest changing immunosuppressive therapy when hyperglycaemia is detected has a role in the management of PTDM (Grade 2B).

5. There is as yet no evidence that newer agents such as belatacept are beneficial in reducing risk of PTDM compared to tacrolimus-based regimens (Grade 1C).

6.2 Areas for Future Research

1. PTDM should be included as a clinical endpoint in randomised controlled trials of new immunosuppressive agents.

2. How do the competing risks of PTDM and rejection compare as risk factors for adverse long-term clinical outcomes?

3. Is there any glycaemic benefit from prolonged-release versus immediate-release tacrolimus formulations?

4. In low immunological risk patients at high risk for PTDM, does a modified immunosuppression regimen (e.g. steroids sparing, CNI conversion) lead to improved short-term (e.g. PTDM, rejection) and long-term (graft function, cardiovascular events, graft loss, mortality) clinical outcomes?

5. Explore the risks and benefits of newer immunosuppressive agents as they enter clinical practice (e.g. PTDM versus other complications).
6.3 Audit recommendations

1. How many transplant units have stratified immunosuppression regimens for renal transplant candidates at increased risk for PTDM?

2. What is the proportion of renal transplant recipients whose immunosuppression medications were modified when PTDM is diagnosed?

3. What is the clinical outcome (e.g. acute rejection, patient/graft survival) in the renal transplant recipients whose immunosuppression protocols is modified following the diagnosis of PTDM?
6.4 Overview

Immunosuppressive therapy used in kidney transplantation can be categorised into induction which includes antithymocyte globulin (ATG), basiliximab and alemtuzimab, or maintenance therapy which includes corticosteroids, calcineurin inhibitors (CNIs - tacrolimus and cyclosporine), azathioprine, mycophenolate mofetil (MMF), the mammalian target of rapamycin inhibitors (mTORi - sirolimus and everolimus), and belatacept. The action of immunosuppressive therapy is to prevent acute rejection and maintain long term transplant function. Steroids, CNIs and mTORi are associated with an increased risk of PTDM.

Immunosuppressive therapy predominates all known transplant specific risk factors for the development of PTDM which is associated with increased cardiovascular risk [1] transplant dysfunction [2] and increased cost [3].

Whilst early guidelines from IEP meeting in 2003 [4], KDIGO 2009 [5] and the Renal Association (RA) endorsed by the British Transplant Society (BTS) in 2010 [6], advocate modifying or switching immunosuppression is necessary to prevent or minimise the risk of development of PTDM, subsequent guidelines from the ICM in 2013 [7] and the RA endorsed by BTS in 2017 [8] advocate that the choice of immunosuppressive therapy should be to primarily prevent rejection rather than preventing PTDM. These conflicting opinions exist as data from large RCTs with long term follow up on the effect of modifications in the immunosuppressive regimens on PTDM are limited. It is notable that most transplant units in the UK follow their own local protocols for immunosuppressive regimens, with no uniform national guidance available.

6.5 Corticosteroids

There is intense debate on risk versus benefit of corticosteroid sparing for the development of PTDM. Two RCTs showed no clear benefits of steroid sparing regimens on decreasing the incidence of PTDM. The first one reported in 2005 on the five year results of a multicentre RCT of early corticosteroid withdrawal (CSWD) versus chronic corticosteroids (CCS), MMF and tacrolimus in 386 kidney transplant recipients. At five years, the proportion of patients with PTDM requiring any therapy was similar between groups (CSWD [21.5%]; CCS [20.9%]) [9]. The second published in 2015 enrolled 277 patients and showed no significant impact of
early steroids withdrawal compared with long term maintenance steroids of 5mg daily,
tacrolimus and MMF on the incidence of PTDM in patients diagnosed with PTDM from six
months to five years of kidney transplantation [10].

A Cochrane systematic review including 7800 renal transplant recipients published in 2017
confirmed no difference in the occurrence of PTDM between steroid withdrawal and steroid
maintenance strategies up to five years post transplantation [11]. It did however show a
significant increase in the risk of acute rejection (AR) with steroid withdrawal either earlier
(by 58%) or later (by 77%) than 14 days post transplantation versus steroid maintenance, but
no association with patient mortality or graft loss.

By contrast, a multicentre RCT including 538 patients followed up for six month post renal
transplantation and showed a significantly reduced incidence of new-onset insulin-
dependent diabetes mellitus (5.4% vs. 0.4%, p=0.003) with steroid-free immunosuppression
[12]. Similarly in a prospective controlled study of 300 renal transplant recipients with three
years follow up, two day steroid withdrawal significantly reduced risk of PTDM without
affecting the incidence of acute rejection, graft function or patient or graft survival [13].

Evidence from a meta-analysis published in 2010 showing steroids sparing benefits on PTDM
risk versus maintenance strategies, countered by an increased risk of rejection after renal
transplantation [14]. This meta-analysis included thirty-four studies of 5,637 patients and
showed that steroid avoidance/withdrawal (SAW) regimens significantly increased the risk
of acute rejection (AR) over maintenance steroids (p<0.0001) but significantly reduced new
onset diabetes (p=0.0006). No significant differences in corticosteroid resistant AR, patient
survival, or graft survival were observed. Serum creatinine was increased and creatinine
clearance was reduced with SAW. Data on the relationship between steroid-free
maintenance regimens and PTDM in a cohort of 25,837 adult kidney transplant patients
published in 2015 concluded that the adoption of steroid-free maintenance
immunosuppression at discharge from kidney transplantation in selected patients was
associated with reduced odds of developing PTDM within 3 years [15].

A subsequent meta-analysis in 2012 of 29 RCT included 5675 patients showed that steroid
avoidance versus steroids maintenance was associated with less frequent PTDM requiring
any treatment, although this decrease was only evident with cyclosporine, not with Tacrolimus [16].

A more recent retrospective analysis with longer follow up of 15 years in 1553 patients post renal transplantation suggested that rapid discontinuation of steroids was associated with reduced onset of PTDM without decreasing patient or graft survival or increased graft dysfunction [17]. Two recent RCTs, Harmony (615 patients) and Advance (1081 patients) also showed evidence of reduction of incidence of PTDM with steroids-sparing regimens [18, 19].

It is possible that the discrepancy of findings of various studies on the effects of steroid withdrawal on the incidence of PTDM may be due to the increased diabetogenicity of cyclosporine or tacrolimus thus reducing any potential benefits of steroids sparing regimens on reducing the incidence of PTDM. It is also possible that high trough level of CNIs is responsible for the absence of beneficial effects of steroids sparing on reducing the incidence of PTDM [20].

The findings of various studies suggest that steroids sparing regimens can be used as a mechanism to reduce risk of PTDM. Longer term data beyond five years is, however, lacking. Additional end points of potential benefits of steroid sparing regimens such as prolonging patient and graft survival will likely to be required to demonstrate efficacy of such regimens versus steroids based therapies.

### 6.6 Calcineurin inhibitors

CNIs have been associated with increased risk of PTDM with tacrolimus being more potent than cyclosporine in reducing insulin secretion in vitro and vivo [21]. In a meta-analysis of 56 studies (including 16 RCTs) showed that risk of PTDM with tacrolimus was 16.6% compared to 9.8% in those received cyclosporine [22]. Similarly a further meta-analysis including data from 30 RCTs with 4102 patients suggested that risk of PTDM was significantly increased in tacrolimus treated recipients at six months and three years [23]. A subsequent large observational study of 527 patients showed that the risk of PTDM at two years was significantly higher in a tacrolimus based regimen versus cyclosporine [21% vs 8%] [24].

The DIRECT RCT included 567 patients comparing tacrolimus and cyclosporine, with PTDM as the primary end point showed that the incidence of PTDM or impaired fasting glucose at six
months post renal transplantation is significantly lower with cyclosporine (26%) than with tacrolimus (33.6%) [25].

A subsequent larger RCT reported on 638 patients with four years follow up and also showed the incidence of PTDM was significantly higher in tacrolimus treated patients [26]. A recent open-label, multicentre, randomized trial included 128 patients testing whether a tacrolimus-based immunosuppression and rapid steroid withdrawal (SW) within 1 week (Tac-SW) or cyclosporine A with steroid minimization (SM) (CsA-SM), decreased the incidence of PTDM compared with tacrolimus with SM (Tac-SM). All arms received basiliximab and mycophenolate mofetil. The 1-year incidence of PTDM in each arm was 37.8% for Tac-SW, 25.7% for Tac-SM, and 9.7% for CsA-SM. Antidiabetic therapy was required less commonly in the CsA-SM arm (p = 0.06), however the AR rate was higher in CsA-SM arm (Tac-SW 11.4%, Tac-SM 4.8%, and CsA-SM 21.4% of patients; cumulative incidence p=0.04). Graft and patient survival, and graft function were similar among arms. Although the authors concluded that in high-risk patients, tacrolimus-based immunosuppression with SM provides the best balance between PTDM and acute rejection incidence, they suggested that tacrolimus based regimen with SM may be used to prevent acute rejection during the early post-transplant period and to replace tacrolimus with cyclosporine in patients with inadequately controlled PTDM in the maintenance phase [27].

Based on the above studies, given the lower risk of PTDM with cyclosporine versus tacrolimus, conversion studies from tacrolimus to cyclosporine followed to assess risk reduction of PTDM. An RCT published recently included 80 patients with 12 months follow up and showed that 39% of patients in the cyclosporine arm were off glucose-lowering medication vs 13% of patients in the tacrolimus arm (p=0.01). The cyclosporine group, decreased HbA1c levels were noted during the 12-month follow-up compared with the TAC group (p=0.002). The risk of AR was not increased, but cyclosporine conversion was associated with a reduction in renal function. The authors concluded that replacement of tacrolimus with cyclosporine significantly improved glucose metabolism and had the potential to reverse diabetes during the first year after conversion and reduced need for glucose-lowering therapy in a significant proportion of patients with PTDM after renal transplantation [28].

The authors subsequently conducted an economic evaluation to support NICE in developing updated guidance on the use of immunosuppression, and suggested that for patients at risk
of diabetes or at risk of complications from diabetes, it may be more effective and cost effective to use cyclosporine, since diabetes is associated with adverse events and increased mortality [29]. However their conclusion was primarily that basiliximab, tacrolimus and MMF are likely to be optimal immunosuppressants (in terms of cost-effectiveness) for the majority of adult kidney transplant recipients in the NHS, and that cyclosporine offered the second-best net health benefit after immediate release-tacrolimus.

Based on the above studies, there are a number of advocates suggesting that modification of immunosuppressive therapy from tacrolimus to cyclosporine in those who develop hyperglycaemia post renal transplantation should be considered [4,5,6].

CNI sparing has emerged as a strategy to reduce risk of PTDM following a meta-analysis by Sharif et al in 2011. The analysis included 56 RCT reporting on 11,337 renal transplant recipients and showed that CNI sparing regimens reduced the incidence of PTDM [30]. A more recent Cochrane meta-analysis review that included 83 studies and 16,156 renal transplant recipients was reported in 2017 [31]. This analysis sub classified CNI sparing studies into four different interventions groups and analysed them as CNI withdrawal or low dose CNI and standard regimens. They suggested, however, no improvement in PTDM rates using CNI sparing regimens.

6.7 mTOR inhibitors

Regimens enabling CNI reduction may be beneficial to reduce the long term unwanted effects of CNIs including risk of PTDM. Although mTORs may be diabetogenic, results from RCTs and meta- analyses have been published to assess its effects as maintenance immunosuppressive therapy post renal transplantation including its effect on the incidence of PTDM.

A meta-analysis published in 2006 included 33 trials reporting on 7114 renal transplant recipients and evaluated mTORi (everolimus and sirolimus) in four different primary immunosuppressive regimens and concluded that there is no differences in incidence of PTDM up to two years post renal transplantation [32].
However, analysis of the larger USRDS dataset reporting on 20,124 renal transplant recipients showed that combinations that included sirolimus, combined with a CNI or MMF or azathioprine were associated with higher risk of PTDM, with the most diabetogenic combination with CNIs [33]. In 16,681 patients who did not change therapy during the first year post renal transplantation, sirolimus was associated with increased risk of PTDM only in the presence of a CNI. A more recent meta-analysis on conversion from CNI to everolimus included 11 RCTs reporting on 1633 patients assessing the efficacy and safety of everolimus for maintenance immunosuppression. The one year follow up data showed lower incidence of PTDM although this was at increased risk of AR at one year [34].

Further data on mTORi and risk of PTDM has come from an RCT which included 613 renal transplant recipients randomised into everolimus plus low dose tacrolimus or MMF plus tacrolimus in de novo renal transplant recipients [35]. The results demonstrated that everolimus facilitates tacrolimus reduction while achieving good renal function and low AR and graft loss rates, with incidence of hyperglycaemia at 12 months of 24.8% in the everolimus and low dose TAC versus 27% of standard tacrolimus and MMF. This suggests that the incidence of PTDM is not increased by the use mTORi in comparison to CNI.

### 6.8 Belatacept

A more contemporary approach to reduce risk of PTDM post renal transplantation is to use CNI sparingly with new agents such as belatacept. This is a parental immunosuppressant that replaces CNI and selectively inhibits T cell activation through co stimulation blockade. In an RCT of 1209 patients randomised to belatacept based regimens versus cyclosporine based regimens, at one year, a lower incidence of PTDM was seen with belatacept [36].

In a meta-analysis of RCTs reporting on 1535 patients comparing belatacept against any other immunosuppression regimen with three years follow up showed patient survival, graft loss, and AR were all similar, but that belatacept treated patients were 28% less likely to have chronic kidney scarring and better GFR that CNI treated recipients, and the risk of PTDM was reduced by 39% [37].

Subsequently, the BENEFIT study appeared to confirm these findings, showing a 43% reduction in the risk of death or graft loss for belatacept based regimens compared with
cyclosporine regimen. In addition, mean eGFR was significantly higher and risk of death or graft loss after seven years was significantly lower for belatacept-treated patients [38]. There was no mention of risk of PTDM in this study.

Comparison of tacrolimus based regimens with belatacept has shown slightly differing results. In a retrospective cohort study using registry data on 50,244 patients, comparing one year clinical outcomes between belatacept- and tacrolimus-treated kidney transplant recipients, belatacept alone was associated with a higher risk of AR, with the highest rates associated with non-lymphocyte-depleting induction [39]. There was no significant difference in rejection rates between belatacept plus tacrolimus and tacrolimus alone. The incidence of PTDM was significantly lower with belatacept plus tacrolimus and belatacept alone versus tacrolimus alone. Similar results were recently obtained from a small RCT in which 40 patients were randomised to belatacept vs tacrolimus in addition to MMF and Pred [40]. The risk of AR was 55 % in the belatacept group vs 10% of the TAC group - no data on risk of PTDM was provided.

### 6.9 Induction agents

A number of studies report on the impact of induction agents on the risk of PTDM. A single-centre retrospective study of 264 renal transplant recipients showed induction with IL-2RA basiliximab was associated with a significantly greater risk of developing PTDM compared to no induction (51.5\% vs. 36.9\%) at 10 weeks post transplantation [41]. This was also seen in a prospective observational study of 439 renal transplant recipients, where PTDM was observed in (16.7\%) of patients without induction and (30.5\%) of patients with basiliximab induction [42]. This may suggest that although basiliximab may reduce AR, it appears to be associated with an increased risk of PTDM.

Meta-analysis of 10 RCTs of 1223 patients looking at induction regimens IL-2RAs, alemtuzumab and rabbit ATG suggests that these agents are not associated with increased risk of PTDM [43]. A further meta-analysis of 446 patients from six RCTs showed similar findings [44].

The table below outlines the PTDM risk of commonly used immunosuppressive regimens.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Post-transplant diabetes mellitus risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Increased</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Increased</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>mTORi</td>
<td>Slightly increased</td>
</tr>
<tr>
<td>Mycophenylate Mofetil</td>
<td>No effect</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>No effect</td>
</tr>
<tr>
<td>Belatacept</td>
<td>Slightly decreased?</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Slightly increased?</td>
</tr>
</tbody>
</table>
7.0 PREVENTION OF PTDM

7.1 Recommendations

6. The risk for development of diabetes should be assessed as part of a pre-transplant work-up for all people being considered for transplantation (Grade 1B).

7. All people awaiting renal transplantation should be educated on the risk of developing PTDM, should be counselled about minimising weight gain using lifestyle measures, and should see a nutritionist with expertise in this area (Grade 1B).

8. Treatment of risk factors for PTDM such as hepatitis C should be considered in patients awaiting transplantation (Grade 1C).

9. In people considered at high risk for the development of PTDM, consideration should be given to immunosuppressive therapy that is less prone to inducing hyperglycaemia but this should be based on individualised risk with immunological status in mind (Grade 1C).

10. All patients deemed at high risk for development of PTDM should be screened yearly for diabetes whilst awaiting transplantation (Grade 1B).

7.2 Areas for future research

1. What is the role of standard risk scores for predicting the development of PTDM?

2. Does intensive lifestyle intervention prevent the development of PTDM?

3. Is there a role for pharmacotherapy (metformin, GLP-1 analogues, orlistat) in the prevention of PTDM?

7.3 Audit recommendations
1. What proportion of patients awaiting transplantation are risk assessed for the development of PTDM?
Risks factors for the development of PTDM are similar to those of T2D and outlined in greater detail in section 4.0. Prevention or delay of T2D is feasible using lifestyle intervention [1-3] or pharmacotherapy [1,2,4-7]. More recently, remission of Type 2 diabetes has been achieved in people with T2D treated with very low calorie diets [8]. There are additional risk factors for PTDM that may be modifiable (for example type of immunosuppression, cytomegalovirus or hepatitis C infection) [9]. Risk scores for the development of T2D are well described (eg QDiabetes) [10]. Chakkera and colleagues suggest a pre-transplant risk score comprising seven variables of older age, planned corticosteroid therapy after transplant, prescription for gout medicine, higher BMI, higher fasting glucose, higher triglycerides, and family history of T2D could predict most cases of PTDM [11]. Other risk scores also evaluated in PTDM include the San Antonio Diabetes Prediction Model and the Framingham Offspring Study-Diabetes Mellitus algorithm [12].

As described in section 6.0, weight gain following transplantation is common, often due to fewer dietary restrictions after transplantation, improved appetite off dialysis, corticosteroid use and inadequate lifestyle changes [13]. Nutritional care for patients undergoing renal transplantation is advocated by KDIGO guidelines, but frequently not given high priority [14]. Dietary intervention may reduce weight gain post-transplantation [15]. Higher weight pre-transplantation is a risk factor for the development of PTDM, and is a target for prevention (see later) [16]. Clinical trials of active versus passive lifestyle intervention in renal transplant recipients are underway [17-19]. Mediterranean Style Diet may be associated with a lower post-transplant diabetes risk [20]. Increased vegetable intake, but not fruit intake, has been associated with reduced risk for PTDM likely due to beneficial effects on components of the metabolic syndrome [21]. The effect of lifestyle modification on PTDM has been tested in a small study and may have an important beneficial effect. Amongst 115 renal transplant recipients, a group with IGT / PTDM were treated with lifestyle modification and exercise advice for six months. 44% of the IGT group went on to have normal glucose tolerance, and 4% developed PTDM. Overall there was a modest reduction (15%) in post prandial glucose excursion in the whole group [22]. A larger study of 130 patients undergoing renal transplantation randomised to active versus passive lifestyle intervention is currently recruiting [17].
There is currently no strong evidence that diet or lifestyle based will prevent or delay PTDM. Nevertheless, as diet and lifestyle change are the cornerstones of diabetes therapy in the non-transplant setting, high priority should be given to dietary intervention to manage hyperglycaemia and weight gain in patients with PTDM.

Bariatric surgery has a potent effect on prevention (or indeed remission) of Type 2 diabetes in high risk patients [23]. In patients in haemodialysis, there may be a role for bariatric surgery to prevent development of diabetes [24,25]. In one series of 24 patients undergoing bariatric surgery whilst on dialysis, pre-operative BMI mean was 41 kg/m\(^2\), and dropped to a mean of 28 kg/m\(^2\), facilitating transplantation in 16 patients subsequently [24].

7.5 Pharmacological intervention

In the non-transplant setting, a number of pharmacological agents have been shown to prevent or delay the onset of Type 2 diabetes in individuals at high risk (for example in people with impaired glucose tolerance (IGT)). Agents used in this circumstance include metformin [1,2,4], rosiglitazone [5], pioglitazone [6], acarbose [7], orlistat [26] and liraglutide [27].

In renal transplantation, there are a small number of studies involving small numbers of patients with pharmacotherapy aimed at preventing the onset of PTDM. A study of 48 patients with stable renal transplants and IGT treated with three months of vildagliptin or pioglitazone led to a significant reduction in two hour glucose concentration [28], but no mention of prevention of PTDM is made. A larger study of sitagliptin to prevent PTDM is currently actively recruiting [29]. One study of metformin in patients with PTDM and impaired glucose tolerance has recruited 19 patients and is awaiting results [30]. Finally, the PRODIG study (Prevention of new onset diabetes after transplantation by a short term treatment of Vildagliptin in the early renal post-transplant period) is a planned French multi-centre randomized controlled trial exploring the benefit of short-term (two months) vildagliptin in non-diabetic renal transplant recipients to prevent the onset of PTDM [31].

As the natural history of PTDM generally starts with severe hyperglycaemia (due to immunosuppressant induced beta cell dysfunction), followed by more modest hyperglycaemia as immunosuppression is tapered, early insulin therapy is frequently
required (see section 6.0). One study aimed to address whether early insulin therapy could be effective in preventing PTDM [32]. This study randomised 50 patients with hyperglycaemia in the first three weeks following renal transplantation to early basal insulin therapy versus standard care and found a 73% lower risk for development of PTDM. The authors suggest that insulin may protect the \( \beta \)-cells from stress hyperglycaemia (glucose toxicity) and calcineurin inhibitor toxicity. Larger studies are awaited.

Hepatitis C is a significant risk factor for the development of PTDM, and clearance of hepatitis C prior to transplantation may be possible with new drugs. A study of 14 patients with hepatitis C treated with \( \alpha \)-interferon prior to renal transplantation showed a lower incidence of PTDM compared to a control group of 40 patients who were untreated [9]. A further study of 16 renal transplant recipients with hepatitis C who received interferon and had a sustained virologic response, showed that none developed PTDM over two years follow up [33].

Choice of immunosuppressive regimen may also reduce risk of PTDM in high risk individuals. In a study of the use of 1209 patients treated with belatacept, a selective c-stimulation blocker, versus standard immunosuppression with cyclosporine A, use of low intensity belatacept was associated with a lower risk for the development of PTDM [34].
8.0 PTDM CONSIDERATIONS IN THE NON-RENAL SETTING

8.1 Recommendations

4. Organ-specific factors should be considered when counselling patients for their risk of PTDM prior to solid organ transplantation (Grade 1B)

5. The diagnosis of PTDM should be consistent across different solid organ transplant settings, with organ-specific caveats in mind to determine the optimal diagnostic test (e.g. accuracy of HbA1c) (Grade 1C)

6. The management of PTDM should be consistent across different solid organ transplant settings, with organ-specific caveats in mind to determine the optimal management strategy (Grade 1B)

8.2 Areas for future research

1. What are the long-term outcomes for solid organ transplant recipients who develop PTDM?

2. Is the evolution on abnormal glucose metabolism post-transplantation different among different solid organ transplant settings?

3. Should solid organ transplant recipients receive the same management intervention strategy?

8.3 Audit recommendations

1. What proportion of non-renal solid organ transplant patients are risk assessed for the development of PTDM prior to transplantation?

2. What proportion of non-renal solid organ transplant patients are screened for post-transplant hyperglycaemia and PTDM?

3. What proportion of patients undergoing non-renal solid organ transplants have good glycaemic control as determined by their individualised glycaemic target?
8.4 Overview

While the overwhelming majority of published articles in the area of PTDM relate to renal transplantation, it is important to consider PTDM in the setting on non-renal transplantation. Shared generic and transplant-specific risk factors mean PTDM remains a significant medical complication after all forms of solid organ transplantation.

While the bulk of PTDM literature is in the setting of kidney transplantation, the burden of PTDM translates across other forms of solid organ transplantation [1]. While general considerations are easily translatable across different solid organ settings, there are some unique aspects to take into consideration with each specific organ with considering the diagnosis, prevention and management of PTDM.

8.5 PTDM after liver transplantation

8.5.1 Epidemiology and outcomes
The risk of developing PTDM after liver transplantation is significant, with registry data suggests rates of up to 40% within five years post-transplantation [1-3]. While liver transplant recipients share the same generic and many transplant-specific risk factors for development of PTDM, there are some unique considerations that lead to such high incidence after liver transplantation. For example, non-alcoholic steatohepatitis (NASH) is making a greater contribution to the burden of end-stage liver disease and patients with NASH often share features of the metabolic syndrome [4]. Transplant registry data from the United States has shown liver transplant recipients are more likely to develop PTDM with versus without a past medical history of NASH [5]. In addition, hepatitis C is a common cause of end-stage liver disease and an independent risk factor for development of PTDM after liver transplantation [6]. The combination of these aetiological factors likely explains why incidence of PTDM is highest after liver transplantation compared to other solid organ allografts [1]. However, no study after liver transplantation has utilised the OGTT for diagnostic purposes and the likely burden of PTDM and pre-diabetes may be higher than expected.

While single centre studies have shown conflicting results with regards to mortality outcome for liver transplant recipients who develop PTDM [3,7], registry data from Taiwan has shown
increased mortality for liver transplant recipients with PTDM [8]. In a retrospective single-centre study of 994 liver transplant recipients from the United States, 16% had transient PTDM and 20% had sustained PTDM after liver transplant surgery with increased cumulative incidence of cardiovascular events and death associated with sustained PTDM [9].

8.5.2 Liver transplant caveats for diagnosis and management
As the liver has a major role in glucose metabolism, hyperglycaemia in early liver transplantation may commonly occur. PTDM diagnostic classification should remain the same for liver transplant recipients, but there are some specific considerations that should be considered. Many liver transplant recipients will have renal impairment and therefore the same precautions are required for interpretation of HbA1c in this setting as per other populations [10]. In addition, interpretation of HbA1c in the context of advanced liver disease may not be appropriate due to altered erythrocyte presentation [11] and therefore should be interpreted with caution if the liver allograft has sub-optimal function.

Management of diabetes in the setting of liver impairment can be difficult as the liver is the major site of metabolism for many anti-diabetic medications. Therefore, it is important to adjust the choice of pharmacological therapy on an individual basis after liver transplantation based upon the functional status of the liver allograft [12].

8.6 PTDM after heart transplantation

8.6.1 Epidemiology and outcomes
Registry data from South Korea and the Netherlands have reported PTDM rates of 25-28% and 20% respectively after 5-years post heart transplantation [13,14], with shared risk factors for its development as other solid organ transplant recipients [15]. Data with regards to outcomes is more limited, due to the limited published literature. For example, diabetes is known to be a risk factor for death within a year of heart transplantation (hazard ratio 1.37, 95% CI 1.15-1.62) but does not distinguish between pre-transplant diabetes versus PTDM [16]. In a South Korean study including 390 heart transplant recipients, patients with PTDM (determined by OGTT) had a similar risk of mortality as those with pre-existing diabetes mellitus, both of which were two-fold higher than heart transplant recipients without diabetes [13].
8.6.2 Heart transplant caveats for diagnosis and management

While there are no specific diagnostic considerations for detection of PTDM in heart transplant recipients, there are management considerations to be considered in the context of heart failure due to sub-optimal heart allograft function. While the majority of pharmacological interventions are safe, the use of thiazolidinediones should be avoided but this may not be a class effect [17]. 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. Glitazones and saxagliptin should probably be avoided in such patients as they may exacerbate heart failure.

8.7 PTDM after lung transplantation

8.7.1 Epidemiology and outcomes

Similar to heart transplantation, a significant proportion of lung transplant recipients develop PTDM. In a prospective single-centre study from Melbourne using OGTTs 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 [18]. Data from the International Society of Heart and Lung Transplant (ISHLT) registry and the United States shows PTDM incidence rates of approximately 30% and 40% among surviving lung transplant recipients by 5-years [19,20]. The incidence of PTDM appears greater in patients with a background of cystic fibrosis, with half of patients having diabetes prior to lung transplantation and half of the remaining individuals developing PTDM after lung transplantation [21]. Outcome data remains 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 hyperglycemia but did not distinguish patients with pre-transplant diabetes versus PTDM [22].

8.7.2 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.
REFERENCES

SECTION 1.0 REFERENCES


SECTION 2.0 REFERENCES


SECTION 3.0 REFERENCES


SECTION 4.0 REFERENCES


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SECTION 5.0 REFERENCES


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SECTION 7.0 REFERENCES


SECTION 8.0 REFERENCES


