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

SUMMARY OF RECOMMENDATIONS

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EPIDEMIOLOGY OF PTDM

Recommendations

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

Areas for future research

1. **Determine the incidence of PTDM longitudinally post-transplantation among different patient cohort groups (eg. age, gender, body mass index, ethnicity).**
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?**

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?**

PATHOGENESIS OF PTDM

Recommendations

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

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?**

Audit recommendations

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

DETECTION OF PTDM

Recommendations

1. **Avoid diagnosis of PTDM in the first six weeks post operatively 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 six weeks post-transplantation using an oral glucose tolerance test (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. **HbA_{1c} ≥6.5% (48mmol/mol) is a suitable diagnostic test in clinically stable solid organ transplant recipients after the first three months post-transplantation. In asymptomatic patients, the test should be repeated after two weeks to confirm the diagnosis (grade 1B).**
6. **Caution with the use of HbA_{1c} 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 HbA_{1c} >6.5% (48mmol/mol) will detect the majority of PTDM cases (Grade 2C).**
8. **Patients awaiting transplant should receive annual glycaemic testing with FPG +/- HbA_{1c}. 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)**

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?**

Audit recommendations

1. **Is there a formal protocol for screening for pre-existing diabetes in people awaiting transplantation?**
2. **What proportion of patients are screened for hyperglycaemia in the immediate post-transplant period?**
3. **What proportion of patients following transplantation undergo yearly HbA_{1c} screening?**

MANAGEMENT OF PTDM

Recommendations

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), 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 (ideally coded as "post-transplant diabetes mellitus"), and offered structured diabetes care, along with regular screening for complications (Grade 1B).**
5. **If patients with a stable eGFR $\geq$30 mls/min/1.73m^2 and BMI $\geq$25 kg/m^2, 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, and doses should be adjusted according to eGFR (Grade 2C)**
7. **SGLT-2 inhibitors should be used with caution in patients with stable eGFR $\geq$30mls/min/1.73m^2 and poor glycaemic control in patients at low risk of urinary tract infection, 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).**

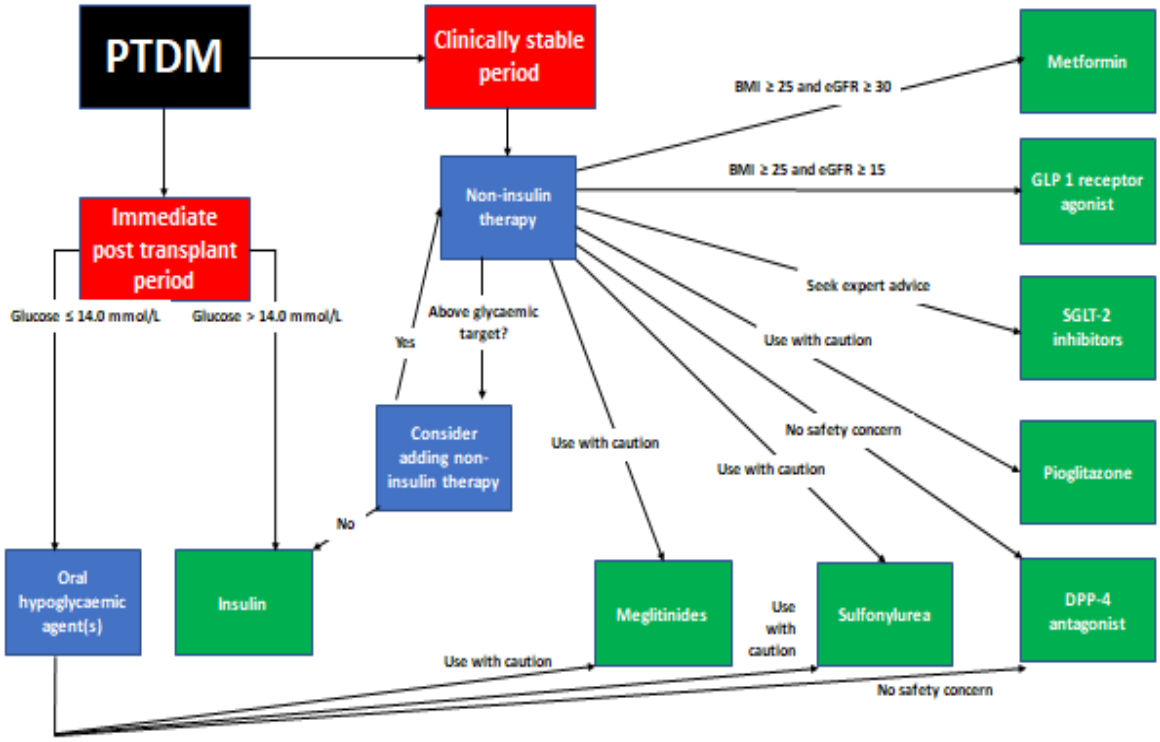
Areas for Future Research

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 in the early or late post-transplant period?**
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?**

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?**

Figure 1. Flow chart for the glycaemic management of post transplant diabetes mellitus (PTDM)



MODIFICATION OF IMMUNOSUPPRESSION TO PREVENT OR TREAT PTDM

Recommendations

1. **Whilst 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).**

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).**

Audit recommendations

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

PREVENTION OF PTDM

Recommendations

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 transplantation should be educated on the risk of developing PTDM, should be counselled about minimising weight gain using lifestyle measures, and should see a dietitian 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).**

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?**

Audit recommendations

1. **What proportion of patients awaiting transplantation are risk assessed for the development of PTDM?**

PTDM CONSIDERATIONS IN THE NON-RENAL SETTING

Recommendations

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 HbA_{1c}) (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)**

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?**

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?**