Supporting physicians in the management of metabolic alterations in adult kidney transplant recipients: a comment on the joint position statement of the Italian Society of Nephrology (SIN), the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID)

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Table 1 Comparison between the Joint Position Statement of the Italian Society of Nephrology (SIN), the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID) for the Management of Metabolic Alterations in Adult Kidney Transplant Recipients, the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline on the Monitoring, Management, and Treatment of KTRs [2] and the Proceedings From an International Consensus Meeting on Post-transplantation Diabetes Mellitus [3]

Joint position statement SIN—SITO—SID (2020)	KDIGO guidelines (2009)	International consensus meeting on PTDM (2014)
1. Screening for post transplant diabetes mellitus (PTDM)^a		
1.1 We recommend screening all non-diabetic KTRs (10000); at least: Perioperatively^b with fasting plasma glucose and bedside capillary glucose (20000); every 3 months for 1 year with fasting plasma glucose and HbA1c and/or oral glucose tolerance test (OGTT)^c (20000); and annually thereafter, with fasting plasma glucose and HbA1c, unless otherwise clinically indicated^c. (20000)		
1.2 We suggest screening for PTDM with fasting glucose, HbA1c and/or OGTT after starting, or substantially increasing the dose, of CNIs, mTORi, or corticosteroids, and when known risk factors for PTDM are identified during follow-up ^d . (20000)	15.1.1: We recommend screening all nondiabetic KTRs with fasting plasma glucose, oral glucose tolerance testing, and/or HbA1c (1C) at least: • Weekly for 4 weeks (2D); • Every 3 months for 1 year (2D); and • Annually, thereafter. (2D) 15.1.2: We suggest screening for NODAT with fasting glucose, oral glucose tolerance testing, and/or HbA1c after starting, or substantially increasing the dose, of CNIs, mTORi, or corticosteroids. (2D)	Change terminology from new-onset diabetes after transplantation back to post-transplantation diabetes mellitus (PTDM) ^a Exclude transient post-transplantation hyperglycaemia from PTDM diagnosis ^b Expand screening tests for PTDM using postprandial glucose monitoring and HbA1c to raise suspicion, while oral glucose tolerance tests remain the most important ^c Identify Patients at Risk for PTDM ^d
2. Managing PTDM or diabetes present at transplantation		
2.1 Immunosuppressive regimen	15.2: Managing nodat or diabetes present at transplantation	Choose and use immunosuppression regimens shown to have the best outcome for patient and graft survival, irrespective of PTDM risk
2.1.1 If PTDM develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. (20000)	15.2.1: If NODAT develops, consider modifying the immunosuppressive drug regimen to reverse or ameliorate diabetes, after weighing the risk of rejection and other potential adverse effects. (Not Graded)	
2.2 Glycaemic targets	15.2.2: Consider targeting HbA1c 7.0–7.5%, and avoid targeting HbA1c ≤ 6.0%, especially if hypoglycaemic reactions are common. (Not Graded)	
2.2.1 We suggest targeting HbA1c 7.0–8.0% (53–64 mmol/mol) and avoiding a target HbA1c < 6.0% (42 mmol/mol), especially if hypoglycaemic reactions are common. (Not Graded)		
2.2.2 We suggest encouraging self-glucose monitoring for KTRs with PTDM in the first months after transplantation and continuing it thereafter in those on insulin or insulin secretagogues, aiming at pre-prandial capillary plasma glucose of 80–130 mg/dL (4.4–7.2 mmol/L) and peak postprandial capillary plasma glucose < 180 mg/dL (10.0 mmol/L) as for the general population with diabetes (Not Graded)		

Table 1 (continued)

Joint position statement SIN—SITO—SID (2020)	KDIGO guidelines (2009)	International consensus meeting on PTDM (2014)
<p>2.3 Insulin therapy</p> <p>2.3.1 In the inpatient setting we recommend initiating insulin therapy for persistent hyperglycaemia starting at threshold > 180 (10.0 mmol/L) and maintaining a target glucose range of 140–180 mg/dl (7.8–10.0 mmol/L) (100000)</p> <p>2.4 Non-insulin hypoglycaemic agents</p> <p>2.4.1 In the outpatient setting we suggest considering the use of glucose-lowering agents according to patient characteristics, renal function and potential drug-drug interactions (<i>Not Graded</i>)</p> <p>2.4.2 We suggest preferring glucose-lowering agents with neutral or beneficial effects on CV and renal outcomes that have been tested in the KTR population (<i>Not Graded</i>)</p> <p>2.5 Aspirin</p> <p>2.5.1 We suggest that, in patients with diabetes, aspirin (65–100 mg/d) use for the primary prevention of CVD be based on CV risk factors, balancing the risk for ischaemic events to that of bleeding. (<i>Not Graded</i>)</p> <p>2.6 Lifestyle interventions</p> <p>2.6.1 We suggest encouraging lifestyle modifications including dietary changes, physical exercise and, in overweight/obese patients, weight loss. (<i>Not Graded</i>)</p> <p>3. Dyslipidaemias</p> <p>3.1 Screening for dyslipidaemias</p> <p>3.1.1 In adult KTRs, we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) (100000)</p> <p>3.1.2 We suggest repeat evaluation of lipid profile 8 (±4) weeks after starting or adjusting treatment, until the target is achieved, and annually thereafter, unless otherwise clinically indicated (<i>Not Graded</i>)</p>	<p>15.2.3: We suggest that, in patients with diabetes, aspirin (65–100 mg/day) use for the primary prevention of CVD be based on patient preferences and values, balancing the risk for ischaemic events to that of bleeding. (2D)</p> <p>16.2: Dyslipidaemias*</p> <p>16.2.1: Measure a complete lipid profile in all adult (≥ 18 years old) KTRs:</p> <p>2–3 months after transplantation</p> <p>2–3 months after a change in treatment or other conditions known to cause dyslipidaemias;</p> <p>at least annually, thereafter</p> <p>16.2.2: Evaluate KTRs with dyslipidaemias for secondary causes</p>	<p>Use strategies for prevention and treatment beyond modification of immunosuppressive regimens^d</p>

Table 1 (continued)

Joint position statement SIN—SITO—SID (2020)	KDIGO guidelines (2009)	International consensus meeting on PTDM (2014)
3.2 LDL targets		
3.2.1 We suggest a $\geq 50\%$ LDL-C reduction from baseline and an LDL-C goal of < 2.6 mmol/L (< 100 mg/dL) for most KTRs (Not Graded)	16.2.2.1: For KTRs with fasting triglycerides ≥ 500 mg/dL (≥ 5.65 mmol/L) that cannot be corrected by removing an underlying cause, treat with:	
3.2.2 We suggest a $\geq 50\%$ LDL-C reduction from baseline and an LDL-C goal of < 1.8 mmol/L (< 70 mg/dL) in KTRs at very high CV risk (e.g. with previous CV events) (Not Graded)	<ul style="list-style-type: none"> •Therapeutic lifestyle changes and a triglyceride-lowering agent 16.2.2.2: For KTRs with elevated LDL-C: if LDL-C ≥ 100 mg/dL (≥ 2.59 mmol/L), treat to reduce LDL-C to < 100 mg/dL (< 2.59 mmol/L)	
3.3. Management of dyslipidaemias	16.2.2.3: For KTRs with normal LDL-C, elevated triglycerides and elevated non-HDL-C: if LDL-C < 100 mg/dL (< 2.59 mmol/L), fasting triglycerides ≥ 200 mg/dL (≥ 2.26 mmol/L), and non-HDL-C ≥ 130 mg/dL (≥ 3.36 mmol/L), treat to reduce non-HDL-C to < 130 mg/dL (< 3.36 mmol/L)	
3.3.1 We suggest that all patients should receive healthy lifestyle advice (Not Graded)		
3.3.2 In adult kidney transplant recipients, we suggest treatment with a statin as first line (20000)		
3.3.3 We suggest ezetimibe or PCSK9 inhibitors as alternative or additional therapy to limit statin dose in KTRs with high LDL-C levels (Not Graded)		
4. Obesity	16.4: Obesity	
4.1 We suggest assessing obesity at each visit (Not Graded). Measure height and weight at each visit to calculate BMI (20000). Measure waist circumference when weight and physical appearance suggest obesity, but BMI is < 30 kg/m ² (20000)	16.4.1: Assess obesity at each visit. (Not Graded) <ul style="list-style-type: none"> •Measure height and weight at each visit, in adults and children •Calculate BMI at each visit •Measure waist circumference when weight and physical appearance suggest obesity, but BMI is < 35 kg/m² 	
4.2 We suggest offering a weight-reduction program including dietary and physical activity recommendations to all obese KTRs (Not Graded). Bariatric surgery could be considered as an option in adult KTRs who have failed to lose weight or to maintain long-term weight loss despite appropriate non-surgical interventions (20000)	16.4.2: Offer a weight-reduction program to all obese KTRs. (Not Graded)	

BMI body mass index, CNI calcineurin inhibitor, CV cardiovascular, CVD CV disease, HbA1c haemoglobin A1c, HDL high-density lipoprotein cholesterol, KDIGO Kidney Disease: Improving Global Outcome, KTRs kidney transplant recipients, LDL low-density lipoprotein cholesterol, mTORi mammalian target of rapamycin inhibitor(s), NODAT new-onset diabetes after transplantation, OGTT oral glucose tolerance test, PCSK9 proprotein convertase subtilisin/kexin type 9, PTDM post-transplantation diabetes mellitus

*These recommendations are based on KDOQI Dyslipidaemia Guidelines [6] and are thus Not Graded The strength of recommendations and the quality of evidence were reported according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Recommendations are classified into one of two grades (grade 1: strong recommendation; grade 2: weak recommendation), while the quality of the evidence is classified into one of four categories (0000, very low; 0000, low; 0000, moderate; 0000, high). Recommendations with no grade were classified as “not graded”

^aThe definition “PTDM” was adopted in the Joint Position Statement (JPS)

^bThe JPS acknowledges that a formal diagnosis of PTDM is best made when patients are stable on their likely maintenance immunosuppression, with stable kidney graft function and in the absence of acute infections, as already recommended [3]

^cThe JPS recognises that, although a diagnosis of PTDM is preferably based on OGTT results, OGTT is time-consuming, and not routinely performed. For this reason, alternative screening methods have been deemed suitable

^dThe JPS suggests screening for PTDM when known risk factors for PTDM are identified during follow-up

^eThe International Consensus agreed that lifestyle modification $>$ oral anti-diabetic therapy $>$ insulin is an appropriate stepwise approach for management of late-PTDM, but with immediate post-transplant hyperglycaemia the reverse is recommended as the most appropriate management [3]

Post-transplant diabetes mellitus, dyslipidaemias and overweight/obesity are extremely common among kidney transplant recipients (KTRs) and may undermine graft and recipient outcomes. With the joint position statement on the management of metabolic alterations in adult KTRs recently issued by the Italian Society of Nephrology, the Italian Society for Organ Transplantation and the Italian Diabetes Society [1], we sought to address the prevention, diagnosis and treatment of metabolic alterations in KTRs in order to support clinical decisions of professionals involved in the management of these patients. The joint position statement was meant to be an update of the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of KTRs [2] and is based on the evidence published since then. When no new evidence was found, indications were based on expert opinion and relevant guidelines for the non-transplant population. In this commentary addressed to an audience of clinical nephrologists, we review the new statements and compare them with the previous recommendations (Table 1) [2].

1. *Screening for post-transplant diabetes mellitus* Post-transplant diabetes mellitus had been previously addressed by the KDIGO guidelines and by a consensus of international experts [3]. Although postoperative hyperglycaemia may be predictive of subsequent alterations of glucose metabolism and should prompt close monitoring during follow-up, a formal diagnosis of post-transplant diabetes mellitus is best made when patients are stable on maintenance immunosuppression, with stable kidney graft function and in the absence of acute infections [3]. As compared with previous guidelines [2], the joint position statement makes a distinction between the screening method (measurement of fasting plasma glucose, bedside capillary glucose, HbA1c or the oral glucose tolerance test [OGTT]) depending on the timing of assessment (perioperatively, in the first year after kidney transplantation or thereafter). Bedside capillary glucose is introduced as one of the suggested methods for the perioperative period, as it may be more sensitive than other tests in detecting patients at risk for post-transplant diabetes. The joint position statement confirms the need for screening for post-transplant diabetes after modifying the immunosuppressive drug regimen, and suggests screening when known risk factors are identified.
2. *Managing post-transplant diabetes mellitus or diabetes present at transplantation* Similar to previous guidelines [2], the joint position statement suggests considering modification of the immunosuppressive drug regimen. While little evidence was available to grade this statement when the KDIGO guidelines were issued, few

studies have been published showing that early steroid withdrawal and switching from tacrolimus to cyclosporine (CsA) or from a calcineurin inhibitor-based immunosuppressive regimen to a mammalian target of rapamycin inhibitor (mTORi)-based immunosuppressive regimen might have some benefit on glucose metabolism, although more studies are needed to address these strategies. Data are also needed to assess the effects of reducing the dose of tacrolimus, CsA or corticosteroids; replacing tacrolimus or CsA with mycophenolate mofetil or azathioprine; reducing the dose or discontinuing a mTORi. Importantly, the choice of modifying the immunosuppressive regimen should always be balanced against the risk of rejection and other potential adverse effects [3].

For KTRs with pre-existing diabetes or post-transplant diabetes mellitus, a less stringent glycaemic target (HbA1c 7–8% or 53–64 mmol/mol) is proposed, as compared with previous guidelines [2], based on a large retrospective study suggesting that hypoglycaemia is particularly detrimental to KTRs, who are at increased cardiovascular risk as compared with the general population. Self-glucose monitoring should be encouraged. In the absence of studies specifically addressing this point, the same capillary glucose targets as for the general population with diabetes are suggested.

The joint position statement also addresses the pharmacological management of diabetes, in both the inpatient and outpatient setting, more in depth than previously done [3]. Insulin therapy is strongly recommended for persistent hyperglycaemia in the inpatient setting, and glycaemic targets are proposed to reduce the risk of adverse outcomes or subsequent post-transplant diabetes mellitus. There was not sufficient evidence to guide recommendations on the choice of glucose-lowering agents in the outpatient setting, although the advent of novel drugs (i.e. glucagon-like peptide 1 receptor agonists [GLP-1RA] and sodium-glucose cotransporter-2 inhibitors [SGLT-2i]) has boosted research in this field, and more evidence will likely become available soon. It was deemed reasonable to consider the choice of glucose-lowering agents according to patient characteristics, renal function and potential drug-drug interactions, preferring those with neutral or beneficial effects on cardiovascular and renal outcomes and that had already been tested in KTRs. No new studies were available on aspirin use for primary prevention in KTRs. As previously suggested [2], the use of aspirin can be considered for the primary prevention of cardiovascular disease based on risk factors, after balancing the risk for ischaemic events to that of bleeding. Further studies are needed since, in KTRs requiring urgent graft biopsy, aspirin may have

the additional disadvantage of increasing the risk of bleeding and/or of delaying the time of biopsy.

Data on lifestyle modifications on prevention and management of metabolic alterations in KTRs were and still are too sparse to support firm recommendations [2, 3]. The joint position statement suggests encouraging lifestyle modifications including dietary changes, physical exercise and, in overweight/obese patients, weight loss. This suggestion was not graded, due to the paucity and low quality of the available evidence. Very recently, the results of a randomised controlled trial were published, suggesting that a 6-month active lifestyle intervention led by renal dieticians did not improve glucose metabolism as compared with passive lifestyle advice after kidney transplantation [4]. These findings should be taken with caution and not discourage physicians from providing lifestyle recommendations, as (1) both the active and passive interventions appeared to improve glucose metabolism to some extent; (2) the active intervention was associated with greater weight and fat mass loss, as well as with a trend towards lower incidence of post-transplant diabetes mellitus. Lack of precise characterisation of baseline glucose metabolism (i.e. normal, impaired fasting glucose or impaired glucose tolerance), different degrees of renal function and the wide time-window following kidney transplantation (3–24 months) and body mass index range might help explain the lack of significant differences between the two interventions. Future studies should address these aspects and include patients at risk for developing post-transplant diabetes mellitus.

3. **Dyslipidaemias** Studies specifically addressing the need for dyslipidaemia screening in adult KTRs are lacking. The joint position statement confirms that initial evaluation of the lipid profile is strongly recommended, as it is non-invasive, inexpensive, and allows determining the type and severity of dyslipidaemia [5, 6]. Similar to previous guidelines, repeat evaluation of lipid profile is suggested after starting or adjusting treatment, until the target is achieved and annually thereafter, unless otherwise clinically indicated. While an LDL goal of < 100 mg/dL (< 2.6 mmol/L) was previously recommended for all KTRs [1], the joint position statement suggests achieving at least a $\geq 50\%$ LDL-C reduction from baseline in all KTRs, but sets different LDL goals based on the cardiovascular risk profile, suggesting that a lower goal of < 70 mg/dL [< 1.8 mmol/L] for KTRs at very high cardiovascular risk. These goals appear to be realistic and of potential benefit. While no specific indications on the pharmacological management of dyslipidaemias were provided previously, the joint position statement suggests statins as first-line lipid-lowering treatment, as there is evidence that these agents might

reduce cardiovascular events in KTRs. Use of ezetimibe or PCSK9 inhibitors may be considered as alternative or additional therapy to limit statin dose, but studies are needed to confirm the efficacy and safety of these agents in KTRs.

4. **Obesity** As in previous guidelines, assessment of obesity is recommended at each visit, although the strength of recommendation is weak due to the limited number of studies addressing this point. As waist circumference may predict long-term survival better than BMI in KTRs, measuring it is suggested when weight and physical appearance suggest obesity, but BMI is lower than the threshold for diagnosing obesity (< 30 kg/m²). At the time the KDIGO guidelines were published, only anecdotal evidence was available to support the use of bariatric surgery in the management of obese KTRs. Several reports have been published since then, although of low quality, and suggest that bariatric surgery in KTRs is effective for weight loss and associated with low rates of complications and mortality. Given the potential benefits of bariatric surgery on graft function, survival, and obesity-related co-morbidities, further studies are needed to better define indications, type of procedure and weight loss targets in the management of obese KTRs.

With the present joint position statement, we sought to provide practical indications to support clinicians in the management of KTRs. The choice of treatment, however, remains individual and depends on several factors such as the expected risk/benefit ratio for each patient, his/her preferences, and the availability of healthcare resources. A strength of this position statement is that the recommendations stemmed from the joint effort of experts in diabetology and metabolism, nephrology, and kidney transplantation, but several gaps still need to be filled to guide decisions. The efficacy and safety of glucose- and lipid-lowering drugs that have recently become available, the role of bariatric surgery and the identification of subpopulations of KTRs who would benefit the most from lifestyle interventions are just some of the important issues that should be urgently addressed.

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Compliance with ethical standards

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