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VIEWPOINT

Management of metabolic alterations in adult kidney transplant recipients: A 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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Abstract Chronic metabolic alterations such as post-transplant diabetes mellitus (PTDM), dyslipidaemias and overweight/obesity significantly impact on kidney transplant (KT) outcomes. This joint position statement is based on the evidence on the management of metabolic alterations in KT recipients (KTRs) published after the release of the 2009 KDIGO clinical practice guideline for the care of KTRs. Members of the Italian Society of Nephrology (SIN), the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID) selected to represent professionals involved in the management of KTRs undertook a systematic review of the published evidence for the management of PTDM, dyslipidaemias and obesity in this setting. The aim of this work is to provide an updated review of the evidence on the prevention, diagnosis and treatment of metabolic alterations in KTRs, in order to support physicians, patients and the Healthcare System in the decision-making process when choosing among the various available options.

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Introduction

Kidney transplant (KT) is the only definitive cure for end-stage renal disease (ESRD). With more than 21,200 and 2100 KTs performed in 2018 in Europe and Italy, respectively [1], KT is by far the most commonly performed transplant procedure. Graft and recipient survival have dramatically improved over the last decades, and the age range for entering the wait list has broadened to include older recipients [2]. In this context, the impact of chronic metabolic alterations on KT outcomes has become increasingly relevant [3]. Post-transplant diabetes mellitus (PTDM), which includes both undiagnosed pre-existing diabetes and new onset diabetes after KT [4], is reported in 10–20% of KT recipients (KTRs) and may severely affect both short- and long-term outcomes in this population [5]. Furthermore, many KTRs have long-standing diabetes that is often the underlying cause of ESRD leading to KT. In KTRs aged ≥60 years presence of diabetes in the later post-transplant period is an independent predictor of increased mortality [6]. Dyslipidaemias and overweight/obesity are also very common metabolic disturbances among KTRs that may undermine graft and/or recipient outcomes [7–9].

Current guidelines on the management of metabolic alterations in KTRs include the 2009 Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline on the monitoring, management, and treatment of kidney transplant recipients [10] and the recommendations based on the proceedings from an international consensus meeting on PTDM [4]. More recently, recommendations on the management of dyslipidaemia in patients with chronic kidney disease (CKD) including KTRs have been endorsed by the Italian Society of Nephrology (SIN) [9].

The College of the Italian Societies of Nephrology and Organ Transplantation (*Collegio SIN-SITO*) for kidney and pancreas transplantation, which has the scope of i) analysing the specific organisational and clinical aspects of kidney and pancreas donation and transplantation activities ii) developing and coordinating research, the exchange of scientific information, professional training, multicentre studies; iii) promoting actions to optimise the clinical care pathways targeted to patients who can benefit from transplantation and transplant patients; and iv) defining guidelines, identified the need to provide updated guidance on the management of metabolic alterations in adult KTRs and promoted the work that led to the development of this document. This joint position statement is based on the evidence on the management of metabolic alterations in KTRs published after the release of the 2009 KDIGO clinical practice guideline for the care of KTRs [10]. Members of the SIN, the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID) selected to represent professionals involved in the management of KTRs undertook a systematic review of the evidence on the management of PTDM, dyslipidaemias and obesity in adult KTRs published in the last 10 years. Only articles published in English were eligible. When no new evidence was found, recommendations were based on expert opinion and previous guidelines [4,10–22]. The aim of this work is to provide an updated review of the evidence on the prevention, diagnosis and treatment of metabolic alterations in KTRs, in order to support physicians, patients and the Healthcare System in the decision-making process when choosing among the various available options. The position statement addresses the management of adult KTRs and is targeted to healthcare professionals involved in KT, particularly nephrologists, diabetologists and transplant surgeons. The position statement does not intend to define a standard of treatment, nor to establish indications or absolute contraindications. Indeed, the choice of treatment is individual, and depends on several factors such as the expected risk/benefit ratio for the individual patient, her/his preferences, and the availability of healthcare resources.

The strength of recommendations and the quality of evidence were reported according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [23]. 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 (ØOOO, very low; ØØOO, low; ØØØO, moderate; ØØØØ, high). Recommendations with no grade were classified as "*not graded*".

Screening for post transplant diabetes mellitus (PTDM)

A diagnosis of PTDM should be made according to the American Diabetes Association criteria, which include glucose (fasting or 2-h during a 75-g oral glucose tolerance test [OGTT]) and HbA1c criteria [4,11]. The available evidence on the optimal screening timing for each criterion is of low quality and is discussed below.

Hyperglycaemia is very common in the early post-operative period after KT [24], with peaks in the afternoon that likely reflect glucocorticoid kinetics [25,26]. In the first 6 weeks after KT, afternoon capillary blood glucose testing might be more sensitive than other tests in detecting patients at risk for PTDM [26]. In addition, bedside capillary glucose ≥200 and fasting plasma glucose (FPG) measured early after KT identify patients at risk for PTDM [27,28], prompting the need for closer monitoring during follow-up. However, many patients with hyperglycaemia in the early postoperative period show significant improvements both in glycaemic control and variability in the following months [25]. Thus, as previously recognized by a consensus of international experts, a formal diagnosis of PTDM is best made when patients are stable on their likely maintenance immunosuppression,

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with stable kidney graft function and in the absence of acute infections [4].

Diagnosis of PTDM is preferably based on OGTT results [4]. Nevertheless, OGTT is time-consuming, and not routinely performed. For this reason, alternative screening methods have been evaluated.

In the initial months after KT (10 weeks–4 months), the specificity of HbA1c $\geq$ 6.5% (48 mmol/mol) for diagnosing PTDM is as high as 96%, but the sensitivity is low (48%) [29]. Lowering the HbA1c threshold to 6.2% (44 mmol/mol) increased the sensitivity by nearly 30% and decreased specificity by 10%. The relatively low sensitivity of HbA1c in the early post-transplant period limits its use as individual screening test. Furthermore, HbA1c should not be used as the only screening test in the first months after transplant, when factors such as post-operative anaemia, erythropoietin use, and blood transfusions may mine its reliability. As such, we suggest using HbA1c in conjunction with FPG to screen for PTDM in the first months following KT. It has also been suggested that a FPG between 5.3 and 6.9 mmol/L, HbA1c $\geq$ 5.8% (40 mmol/mol), or a FPG $\geq$ 5.0 mmol/L combined with HbA1c $\geq$ 5.7% (39 mmol/mol) in the early post-transplant period (10 weeks) should prompt an OGTT in order to increase the likelihood of detecting undiagnosed PTDM [30].

As OGTT for diagnosing PTDM at 10 weeks post-transplantation has demonstrated superiority *versus* HbA1c with regard to prediction of long-term outcomes (i.e. mortality) in patients without overt diabetes [31], we suggest considering performing an OGTT 2–3 months following KT to screen for PTDM, particularly in those KTRs with combined FPG $\geq$5.0 mmol/L (90 mg/dL) and HbA1c $\geq$ 5.7% (39 mmol/mol) [30].

In a retrospective analysis of nearly 500 KTRs without known diabetes who underwent comprehensive assessment of glycaemic status at one year after transplant, including HbA1c, FPG and OGTT, using HbA1c alone ($\geq$6.5% or 48 mmol/mol) resulted in a specificity of 97% and sensitivity of 43% [32]. This finding is in line with those of a systematic review and metanalysis showing that HbA1c $\geq$ 6.5% (48 mmol/mol) had a sensitivity of 40% and specificity of 94% for diagnosing PTDM one year after KT [29]. Combining FPG and HbA1c criteria for diagnosing PTDM captured almost all patients with persistent PTDM (area under the receiver operating characteristics [AUROC] *versus* OGTT 0.86). After the first year post-transplantation, during which PTDM incidence is the greatest [33–37], continuous screening is recommended, at least annually. In fact, glucose metabolism after transplantation is highly dynamic, with glucose metabolism either deteriorating or improving over time in individual patients even after the first year [38], highlighting the need for continuous screening. Although studies with larger sample size and longer follow-up are needed to better evaluate the diagnostic accuracy of FPG and HbA1c after the first year following KT, it seems reasonable to screen patients with FPG and HbA1c annually, unless otherwise indicated based on clinical conditions.

Finally, we suggest screening for PTDM after initiating or substantially increasing the dose of potentially diabetogenic drugs commonly used in the management of KTRs (e.g. steroids, calcineurin inhibitors and HMG CoA reductase inhibitors) [5,39], as well as when known risk factors for PTDM (e.g. central obesity or significant weight gain, increasing age, hypomagnesaemia, HCV and cytomegalovirus infections) [5,39] are detected.

1 We recommend screening all non-diabetic KTRs, at least:
- perioperatively with fasting plasma glucose and bedside capillary glucose (2ØØOO);
- every 3 months for 1 year with fasting plasma glucose and HbA1c and/or oral glucose tolerance test (OGTT) (2ØØOO); and
- annually thereafter, with fasting plasma glucose and HbA1c, unless otherwise clinically indicated. (2ØØOO)

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. (2ØOOO)

CNI, calcineurin inhibitor; HbA1c, haemoglobin A1c; KTRs, kidney transplant recipients; mTORi, mammalian target of rapamycin inhibitor(s); PTDM*, new-onset diabetes after transplantation.*

Managing PTDM or diabetes Present at transplantation

Immunosuppressive regimen

At the time the KDIGO guidelines were published, there were no RCTs testing whether changing to different immunosuppressive regimens could reverse or ameliorate PTDM [10]. The KDIGO guidelines acknowledged that, given the associations of PTDM with CsA, tacrolimus, mTORi and corticosteroids, it was plausible that reducing or eliminating these immunosuppressive medications could reverse or ameliorate PTDM. Since then, few studies have been conducted to establish the benefits and harms of altering the immunosuppressive medication regimen in response to the development of PTDM.

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Changes in immunosuppressive medications that have been assessed in either randomized or retrospective controlled studies include:

i) **Conversion from tacrolimus to cyclosporine.** Significantly greater incidence rates of PTDM were reported with high-level tacrolimus (trough 8–12 lg/L) and low-level sirolimus (3–7 μg/L) both *versus* cyclosporine plus MMF and low-level tacrolimus (trough 3–7 μg/L) and high-level sirolimus (8–12 μg/L) in KTRs subjected to rapid discontinuation of prednisone, suggesting that high-dose tacrolimus might be associated with diabetogenic effects [40]. In a small case series, conversion of KTRs with PTDM from tacrolimus to cyclosporine improved fasting plasma glucose in the short term (6 months), but the benefit was lost thereafter [41]. More recently, a randomized prospective study showed that conversion from tacrolimus to cyclosporine was associated with the reversal of PTDM in a significantly higher proportion of patients (34% *versus* 10%) at 12 months [42]. Conversion to cyclosporine was also associated with better glycaemic control (HbA1c), and significantly more patients free of glucose-lowering therapy, with no increase in the incidence of acute graft rejection. Nevertheless, patients switched to cyclosporine exhibited a reduction in renal function, a mild elevation in LDL cholesterol, and a numerically higher incidence of infectious episodes. Finally, switch to CsA was mostly effective in milder forms of PTDM, whereas it was less so in patients with PTDM requiring antihyperglycaemic drugs.

ii) **Conversion from CNI to mTORi.** A *post-hoc* analysis of two large randomized trials (ZEUS and HERAKLES) found no difference in the incidence or severity of PTDM in patients who were converted early post-transplant from a CsA-based regimen to everolimus, nor in the progression of pre-existing diabetes [43]. There is some evidence that switching from a CNI-based immunosuppressive regimen to an mTORi-based immunosuppressive regimen might lead to remission of PTDM [44].

We could not find any published reports on the effects of reducing the dose of tacrolimus, CsA or corticosteroids; replacing tacrolimus or CsA with MMF or azathioprine; reducing the dose or discontinuing a mTORi on PTDM. One small retrospective, non-controlled trial showed that switching patients with PTDM from methylprednisolone to everolimus on top of tacrolimus and MMF did not worsen HbA1c over time [45]. An extension of this trial showed a significant decrease in HbA1c levels 9 months after conversion from methylprednisolone to everolimus [46]. Furthermore, at 12 months HbA1c was <6.5%, and renal function remained stable.

As for corticosteroids, **steroid avoidance or early withdrawal** has been advocated as a potential strategy to reduce the incidence of PTDM. Rapid discontinuation of prednisone (5 days after KT) was associated with significantly lower incidence rates of PTDM in KTR *versus* historical controls on prednisone maintenance therapy [47]. The authors of a Cochrane review that assessed the benefits and harms of steroid withdrawal or avoidance for KTRs concluded that it was not possible to clearly demonstrate a reduction in PTDM within five years after transplantation for steroid withdrawal or avoidance in adult KTRs [48]. There was, however, a significant 77% and 58% increase in acute rejection after steroid withdrawal or avoidance, respectively. More recently, a discrete event simulation based on data from over 55,000 KTRs in the United States suggested that strategies of 6-and 12-month steroid withdrawal after kidney transplantation might reduce the rates of PTDM and cardiovascular (CV) events with no worsening of acute rejection or graft loss rates compared with steroid maintenance [49]. Furthermore, in a 6-week randomized study that compared two prolonged-release tacrolimus corticosteroid minimization regimens, incidence of PTDM was similarly low in the two treatment arms (17.4% *vs*. 16.6%; P = 0.579), but the 10-day steroid tapering regimen in conjunction with prolonged release tacrolimus plus MMF had a lower incidence of biopsy-proven acute rejection *versus* a single bolus of steroid in conjunction with prolonged-release tacrolimus plus MMF [50].

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. (2ØØØO)

Glycaemic targets

Tight blood sugar control reduces the risk of developing microvascular diabetes complications both in type 1 and type 2 diabetes [51–54], and the benefits associated with good glycaemic control persist over time [55–57]. Similarly, a reduction in CV events has been reported both in patients with type 1 and type 2 diabetes subjected to early intensive glycaemic control decades after the intervention [57–60].

Recent European and American guidelines on the management of diabetes state that a reasonable HbA1c goal for many adults with diabetes is <7% (53 mmol/mol) [12,16]. More stringent goals (e.g. <6.5% or 48 mmol/mol) might be suggested for selected patients if this can be achieved without significant hypoglycaemia or other adverse effects of treatment (i.e., polypharmacy). On the

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other hand, less stringent goals (up to <8–9% [64–75 mmol/mol]) may be appropriate for patients with a history of severe hypoglycaemia, limited life expectancy, advanced microvascular or macrovascular complications, multiple comorbidities, or long-standing diabetes in whom the goal is difficult to achieve [12,16]. To the best of our knowledge, only one study addressed the issue of glycaemic targets in diabetic KTRs since the publication of the KDIGO guidelines [61]. In this large retrospective cohort study of KTRs who underwent transplantation due to diabetic nephropathy, those with HbA1c between 7.6% and 8.6% (60 and 70 mmol/mol, mean 8.1 ± 0.3% [65 ± 2.4 mmol/mol]) had the best graft outcomes. Based on the above, and considering that KTRs are at increased CV risk as compared with the general population, it seems reasonable to suggest an HbA1c target of 7–8% (53–64 mmol/mol) [62].

HbA1c may be unreliable indicator in the early post-transplant period [3,4]. Self-glucose monitoring should be encouraged for KTRs with PTDM in the first months after transplantation and continued 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 [12].

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 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*)

Insulin therapy

Hyperglycaemia early after kidney transplantation is very common [3,4], and is associated with subsequent development of PTDM [27,63–65] and graft failure [64–66]. More in general, hyperglycaemia in hospitalised patients, with or without diabetes, is associated with adverse outcomes including increased rates of infection and mortality, and longer hospital length of stay [67]. Appropriate glycaemic control in the hospital setting can reduce the risks and improve outcomes [14].

In non-diabetic KTRs participating in a randomized controlled trial assessing the effectiveness and safety of continuous subcutaneous insulin lispro infusion (CSII, pre-supper BG target 110 mg/dL) as compared to basal insulin treatment (pre-supper BG target 110 mg/dL) and standard therapy (i.e. short-acting insulin lispro aiming at pre-lunch and pre-supper blood glucose values < 200 mg/dL), CSII resulted in significantly lower blood glucose levels during the first week after kidney transplantation, as compared to a basal insulin isophane regimen and to standard therapy for most time points [68]. However, longer term results of this study have not been published yet. Another randomized controlled trial that assessed intensive peri- and post-transplant insulin therapy (aiming at a target blood glucose < 121 mg/dL [6.7 mmol/L] on discharge) in KTRs with type 1 or 2 diabetes did not reduce incidence of delayed graft function but increased the incidence of hypoglycaemia (but not severe hypoglycaemia) [69]. Furthermore, this regimen was associated with an increased number of rejection episodes compared with standard insulin therapy (subcutaneous insulin with a basal plus bolus regiment aiming at a blood glucose < 180 mg/dL [10 mmol/L] on discharge) [69]. Finally, in a third study non-diabetic KTRs were randomly assigned to immediate-postoperative isophane insulin for evening blood glucose ≥140 mg/dL (treatment group) or short-acting insulin and/or oral antidiabetic agents for blood glucose ≥180–250 mg/dL (standard therapy) [70]. KTRs in the treatment group had lower blood glucose values during the hospital stay, and 73% lower odds of PTDM than the control group throughout the 12-month follow up. At one year, all patients in the treatment group were insulin-independent, whereas nearly one third of controls required antidiabetic agents.

It seems reasonable to suggest initiating early insulin treatment insulin therapy for persistent hyperglycaemia starting at threshold >180 (10.0 mmol/L) and maintain a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) as in the general inpatient population [14].

1 In the inpatient setting we recommend initiating insulin therapy for persistent hyperglycaemia starting at threshold >180 (10.0 mmol/L) and maintain a target glucose range of 140–180 mg/dL (7.8–10.0 mmol/L) (1ØØØO)

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Non-insulin hypoglycaemic agents

The 2009 KDIGO guidelines did not provide any specific recommendation to guide treatment choices for PTDM [10]. However, over the past decade there has been a paradigm shift in the management of diabetes, due to the advent of novel drugs (i.e. glucagon-like peptide 1 receptor agonists [GLP-1RA] and sodium-glucose cotransporter-2 inhibitors [SGLT-2i]) that have been shown able to modify CV risk and other important outcomes, including the progression of chronic kidney disease (CKD) in patients with type 2 diabetes [71]. Furthermore, more evidence is now available to help clinicians when treating KTRs with PTDM.

International guidelines recommend metformin as he first-line therapy for most individuals with diabetes, unless contraindicated or not tolerated [71]. As metformin is cleared by the kidneys and may increase the risk of lactic acidosis, its use in patients with impaired kidney function has been discouraged in the past. However, the European Medicines Agency recently lowered the glomerular filtration rate (GFR) threshold below which metformin should not be used, and the drug may now be prescribed to stable patients with moderately reduced kidney function (GFR 30–59 mL/min) [72]. The maximum recommended dosage in patients in patients with eGFR <45 mL/min is usually 1000 mg/day [73]. Moreover, transplant recipients on metformin should be instructed to temporarily withdraw the drug in conditions of pending dehydration or when they undergo contrast media investigations or any other situation that predisposes to an increased risk of acute graft dysfunction [73,74]. A large retrospective cohort study conducted in the U.S.A. investigated the frequency of metformin use and its association with patient and graft survival among KTRs [75]. The authors found that nearly 40% of KTRs with a metformin prescription had creatinine levels above the threshold recommended by the Food and Drug Administration. Nevertheless, no patient or allograft survival disadvantage associated with metformin use. A pilot randomised controlled trial of metformin in prediabetes after KT is currently ongoing [76].

A Cochrane review published in 2017 specifically evaluated the efficacy and safety of pharmacological glucose lowering interventions KTRs with diabetes [77]. It encompassed 7 randomised controlled trials, including nearly 400 KTRs. Antihyperglycaemic medications examined included insulin (intensive *versus* less intensive regimens), DPP4 inhibitors (vildagliptin, sitagliptin), and pioglitazone, with variable results. In particular, intensive insulin regimens were associated with neutral or even negative effect on rejection rates, and more hypoglycaemic episodes. Studies on DPP-4 inhibitors showed neutral effects on kidney graft survival and renal function, better glycaemic control *versus* placebo and comparable effect *versus* insulin glargine. Furthermore, the safety profile and incidence of hypoglycaemia were low and similar to placebo. Pioglitazone in conjunction with insulin therapy was more effective than insulin alone in lowering HbA1c, and was not associated with increased hypoglycaemia. The authors of the systematic review, however, concluded that available data were limited and of low or very low quality.

More recently, the role of newer drugs in the management of PTDM has also been assessed. A small retrospective case series of KTRs treated with the GLP-1RA liraglutide suggested that this drug might be safe and effective for treating PTDM [78]. Two studies have assessed the role of SGLT-2i in the management of PTDM. The first study was a small, single-arm pilot trial that enrolled 25 KTRs with PTDM (20 had pre-existing diabetes) who were prescribed canagliflozin on top of standard antihyperglycaemic treatment [79]. Canagliflozin was well tolerated, and significantly reduced blood pressure and HbA1c, without affecting renal function nor tacrolimus levels. A recent randomized controlled trial of empagliflozin in KTRs with PTDM demonstrated significantly greater reductions in HbA1c, body weight, BMI, and uric acid with empagliflozin *versus* placebo [80]. The magnitude of HbA1c reduction was greater in those with baseline HbA1c >8% (64 mmol/mol). Empagliflozin was well tolerated, with no apparent interactions with immunosuppressants.

Although further evidence is needed to support routine use of SGLT-2i in KTRs with PTDM, these drugs are associated with both CV and renal protective effects [81,82], and may therefore be preferred over other agents that are not associated with such beneficial effects and have not been tested in the KTR population. On the other hand, because of their mechanism of action, these drugs may be less effective in reducing HbA1c in patients with impaired renal graft function [83]. Finally, in choosing the most appropriate glucose-lowering agent, drug–drug interactions should always be taken into account [84].

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 (*Not Graded*).
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 (*Not Graded*)

Aspirin

We could find no studies assessing the benefit and/or harm of low-dose aspirin for the primary prevention of CVD in KTRs with PTDM published after the KDIGO guidelines were issued.

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The recent European Society of Cardiology (ESC) Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the European Association for the Study of Diabetes (EASD) state that, in patients with diabetes at high/very high risk, aspirin (75–100 mg/day) may be considered in primary prevention in the absence of clear contraindications [16]. This statement is based on the findings of the ASCEND study, which demonstrated a lower percentage of serious vascular events in patients with diabetes and no evidence of CV disease treated with aspirin *versus* placebo (8.5% *vs.* 9.6%; rate ratio, 0.88; P = 0.01) [85]. Similarly, the 2019 ADA Standards of Care for Diabetes acknowledge that the aspirin-associated absolute decrease in events depends on the underlying CV risk, and state that low-dose aspirin may be considered primary prevention strategy in those with diabetes who are at increased CV risk, after discussing with the patient on the benefits *versus* increased risk of bleeding [13]. When compared to the general population, in KTRs requiring urgent graft biopsy aspirin may have the additionally disadvantage of increasing the risk of bleeding and/or of delaying the time of biopsy.

Aspirin for primary prevention is not recommended in patients with diabetes at moderate CV risk. When low-dose aspirin is used, proton pump inhibitors should be considered to reduce the risk of gastrointestinal bleeding [86,87].

Individuals with diabetes and CV disease, or diabetes with target organ damage, or diabetes with three or more major risk factors, or with a diabetes duration of >20 years are at very high CV risk. Patients with diabetes duration ≥10 years without target organ damage plus any other additional risk factor are at high CV risk. Young patients (type 1 diabetes aged <35 years or type 2 diabetes aged <50 years) with diabetes duration <10 years, without other risk factors, are at moderate risk [16].

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 ischemic events to that of bleeding. (*Not Graded*)

Lifestyle interventions

Weight gain is common in the first months after KT. Although steroid therapy is known to contribute to post-transplant weight gain [88,89], lifestyle factors such as diet and physical activity play an important role [90]. In addition, the association between physical inactivity and poor outcomes in KTRs is well established [91]. Low levels of physical activity are associated with increased CV and all-cause mortality, as well as with the metabolic syndrome and increased insulin and triglyceride levels [92]. Furthermore, low physical activity is also associated with abnormalities of glucose metabolism in KTRs [93].

International guidelines on the management of type 2 diabetes acknowledge that increasing physical activity improves glycaemic control, and should be encouraged in all people with type 2 diabetes [71]. More specifically, the European Society of Cardiology (ESC) – European Association for the Study of Diabetes (EASD) 2019 joint guidelines on diabetes, pre-diabetes, and cardiovascular diseases recommend moderate-to-vigorous physical activity, notably a combination of aerobic and resistance exercise, for ≥150 min/week for the prevention and control of diabetes, unless contraindicated, such as when there are severe comorbidities or a limited life expectancy [16].

Unfortunately, there is a paucity of high-quality research on the effects of physical activity on cardiometabolic outcomes in KTRs, with most evidence being anecdotal or from small observational studies. A systematic review and meta-analysis of randomized controlled trials of exercise training in solid organ transplant recipients showed no significant improvements in exercise capacity or CV risk factors such as incidence of new-onset diabetes after transplantation, but all effect estimates were very imprecise [94]. More recently, both aerobic and resistance training were shown to be well tolerated, and to improve arterial stiffness and cardiorespiratory fitness in KTRs [95,96], suggesting that the exercise-associated benefits observed in the general population could also apply to KTRs. The preliminary results of a multicentre, controlled, prospective, nonrandomized study that enrolled solid organ transplant recipients (21 KTRs) indicate that supervised personalized physical activity for one year is associated with significant reductions in body mass index [97].

One non-randomized prospective trial addressed the effect of lifestyle modification (comprising an exercise program and weight loss counselling) in renal transplant recipients with either PTDM or impaired glucose tolerance, demonstrating a significant improvement 2-h postprandial glucose levels after a mean follow-up of 8.2 months [98]. Conversely, only a significant reduction in percent fat mass with no improvement in cardiometabolic risk factors (e.g. blood pressure, fasting and 2-h plasma glucose, HbA1c) was observed in KTRs with different glycaemic status (normal, impaired fasting glucose, impaired glucose tolerance, diabetes) subjected to 16 weeks of resistance training (45–60 min 3 times per week) *versus* standard care (no structured exercise) [99]. Finally, in a study that assessed the effect of a 90-day pedometer-based physical activity intervention on several metabolic parameters, KTRs in the physical activity cohort were less likely to have impaired fasting glucose at the end of the intervention *versus* those in the usual care cohort (20.7% *vs.* 30.9%,

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p = 0.04). However, no significant difference was found either at 4 or 12 months in weight gain, incidence of PTDM, lipids, or eGFR [100].

While the 2009 KDIGO guidelines did not provide specific dietary recommendations for the management of PTDM [10], the nutritional management of diabetes mellitus in adult KTRs was addressed by the 2010 Caring for Australasians with Renal Impairment (CARI) guidelines [15]. However, the CARI guidelines acknowledged there were no published studies up to September 2006 examining the safety and efficacy of dietary interventions for the prevention and management of diabetes in adult KTRs. We could not find any studies published since September 2006 specifically addressing nutrition therapy in KTRs with PTDM. In a longitudinal cohort study that assessed the prospective associations of fruit and vegetable intake with risk of PTDM in stable KTRs, vegetable (but not fruit) intake was associated with lower risk of PTDM, suggesting that higher vegetable intake might be beneficial for PTDM prevention [101]. A multicentre randomised controlled trial to compare the outcomes of usual care to the effects of exercise alone, and exercise combined with dietary counselling, on physical functioning, quality of life and post-transplantation weight gain in KTRs is currently ongoing [102].

While awaiting for more specific evidence on dietary interventions in the KT setting, it is reasonable to follow the nutritional recommendations developed for the general population with diabetes [16,17]. Weight loss interventions in overweight and obese KTRs are addressed in OBESITY of this document.

1 We suggest encouraging lifestyle modifications including dietary changes, physical exercise and, in overweight/obese patients, weight loss. (*Not Graded*)

Dyslipidaemias

Screening for dyslipidaemias

Cardiovascular disease is one of the leading causes of death among KTRs [103,104]. Despite reductions in CV disease and mortality after KT as compared with patients who remain on dialysis, CV risk is higher than in the general population [105–107]. Both traditional and non-traditional CV risk factors contribute to the increased risk observed in this population, with some risk factors being exacerbated by certain immunosuppressive drugs. Cyclosporine, corticosteroids, sirolimus, and everolimus negatively impact on lipid profile, generally to a greater extent than tacrolimus, whereas no significant effect is reported with mycophenolate or azathioprine [108]. Due to a paucity of data on CV risk assessment and interventions aimed at reducing CV risk in KTRs, strategies to reduce CV risk are largely extrapolated from other patient populations. Individuals with chronic kidney disease (CKD) are considered at high (stage 3 CKD) or very-high risk (stage 4–5 CKD or on dialysis). In KTRs, the risk of atherosclerotic CV disease is determined, at least in part, by the increased risk associated with CKD itself. As such, aggressive management of CV risk factors, including atherosclerotic dyslipidaemia, is mandatory. Despite the lack of studies specifically addressing the need for dyslipidaemia assessment in adult KTRs, we agree with the KDIGO Clinical Practice Guideline for Lipid Management in CKD in recognizing that initial evaluation of the lipid profile is non-invasive, inexpensive, and likely beneficial, as it allows determining the type and severity of dyslipidaemia [21,109].

In the absence of evidence specifically relating to lipid monitoring in KTRs, it is reasonable to adopt the same recommendations issued by recent international guidelines on lipid management in the general population [18,20]. Repeat evaluation is suggested 4–12 weeks after starting or adjusting treatment, in order to assess patient adherence and treatment efficacy. Once the treatment target is achieved, periodic annual remeasurements are suggested, unless more frequent evaluation is clinically indicated (e.g. change in immunosuppressive regimen or initiation of medications known to interfere with current lipid-lowering treatment).

1 In adult KTRs, we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) (1ØØOO)
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 (*Not Graded*)

Ldl targets

In the Assessment of LEscol in Renal Transplantation Study (ALERT) trial, a 32% reduction from baseline in LDL cholesterol levels by fluvastatin, with a mean difference of 39 mg/dL (1.0 mmol/L) between the treatment and the placebo arms throughout the study, led to a significant

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reduction in the risk of cardiac death or nonfatal myocardial infarction (MI), and a non-significant reduction in coronary death or non-fatal MI compared with placebo [110]. Subgroup analysis of patients with systemic lupus erythematosus showed a LDL-reduction of nearly 30% and a borderline significant 73.4% reduction in the risk of major cardiac events (P = 0.064) [111]. A systematic review and metanalysis of randomized trials that assessed the benefits and harms of statin therapy for CKD patients, the mean absolute reduction from baseline in LDL cholesterol was 43.5 mg/dL (1.1 mmol/L) in KTRs, the magnitude of reduction being similar across different stages of CKD (not on dialysis, dialysis, KT) [112]. While statin therapy reduced major CV events in CKD patients not on dialysis, the effects in KTRs were uncertain (RR 0.84 [CI 0.66–1.06]), in lower-quality evidence. Similar effects were found for MI and stroke (RR 0.70 [CI 0.48–1.01] and RR 1.18 [0.62–2.24], respectively, in KTRs). A more recent Cochrane review that specifically addressed statin use in KTRs yielded similar results [113]. Of note, the statin dose was relatively low in the studies included in these metanalyses and, due to insufficient information, it was unclear whether treatment benefits from statins were dependent on reductions in serum cholesterol.

Finally, in a 12-month randomized open-label, prospective study, statin treatment (rosuvastatin or atorvastatin 10 mg) did not delay the progression of coronary artery calcification (CAC) in KTRs [114].

In light of the available data, it appears that reductions in LDL cholesterol of at least 30% are needed to achieve some CV benefit in KTRs. In the absence of trials addressing the relationship between LDL reduction and CV events in this population, it is reasonable to follow recommendations issued for patients at high or very high risk in the general population.

Current international guidelines agree on achieving ≥50% reductions in LDL cholesterol in high- and very-high risk patients (those with documented atherosclerotic CV disease, type 1 or type 2 diabetes, very high levels of individual risk factors, or CKD) [18,20]. However, the European guidelines set more stringent treatment targets (LDL cholesterol <70 mg/dL [<1.8 mmol/L] and <55 mg/dL [<1.4 mmol/L] for high- and very-high risk patients, respectively) as compared with American guidelines (LDL cholesterol <100 mg/dL [<2.6 mmol/L] and <70 mg/dL [<1.8 mmol/L] for high- and very-high risk patients, respectively). Given the potential risk of increasing the dose of lipid lowering medications due to potential drug–drug interactions [115], and the lack of evidence specifically relating to the KTR population, a reduction ≥50% from baseline LDL cholesterol levels aiming at LDL cholesterol at least <100 mg/dL (<2.6 mmol/L) and <70 mg/dL (<1.8 mmol/L) for high- and very-high risk patients, respectively, appears to be of potential benefit and more realistic.

1 We suggest a ≥50% LDL-C reduction from baseline and an LDL-C goal of <2.6 mmol/L (<100 mg/dL) for most KTRs (*Not Graded*).
2 We suggest a ≥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*)

Management of dyslipidaemias

We could not find studies specifically addressing the role of lifestyle interventions in the management of dyslipidaemia in KTRs. In the absence of high quality studies on the effect of lifestyle interventions in KTRs with dyslipidaemia, and taking into account the evidence for the benefit of providing lifestyle interventions for the treatment of dyslipidaemia in the general population, it is reasonable to follow the lifestyle recommendations issued for the general population [18,20].

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are the pillar of lipid-lowering management, providing significant reductions in CV morbidity and mortality in the general population [116]. Trials that assessed the role of statin therapy (either atorvastatin or rosuvastatin) in patients on haemodialysis, with or without diabetes, failed to demonstrate a reduction in the risk of CV disease [117,118]. However, in the Study of Heart and Renal Protection (SHARP) treatment with simvastatin plus ezetimibe was effective in reducing CV events individuals with CKD [119]. In general, it appears that the CV benefit of reducing LDL cholesterol with statin therapy decreases with worsening renal function [120], highlighting the importance of treating CKD patients when GFR is moderately reduced and the likelihood of achieving clinically relevant reductions in LDL cholesterol is higher, and that more aggressive treatment is needed to achieve similar benefits as in individuals without CKD.

The ALERT trial demonstrated a significant reduction in the risk of cardiac death or nonfatal myocardial infarction (MI), although it failed to demonstrate a significant effect on coronary death or non-fatal MI compared with placebo [110]. Of note, in a subgroup analysis of the ALERT trial, statin treatment was associated with a more pronounced reduction in major CV events, as well as with a significant reduction in cardiac death in KTRs with the metabolic syndrome as compared with those without [121].

A Cochrane systematic review of the benefits and harms of statins in KTRs (n = 3465) free of coronary heart disease

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concluded that statins (generally at a simvastatin dose equivalent to 10 mg/d) may reduce CV mortality (RR 0.68, 95% CI 0.45 to 1.01) and, based on the ALERT trial, major CV events (RR 0.84, 95% CI 0.66 to 1.06) and fatal or non-fatal MI (RR 0.70, 95% CI 0.48 to 1.01) [113]. However, the magnitude of these effects remains uncertain, as confidence intervals were wide and included the possibility of no effect. Statin treatment had uncertain effects on all-cause mortality (RR 1.08, 95% CI 0.63 to 1.83). Similar findings had been reported by the same authors in a previous systematic review and metanalysis [112]. More recently, another metanalysis of randomized trials of statin *versus* placebo across CKD stages including KT confirmed that statins may reduce CV mortality in KTRs, but too few KTRs have been included in lipid lowering trials to draw firm conclusions [122].

A retrospective longitudinal cohort study demonstrated that KTRs on statin therapy $\geq$50% of the post-transplant follow-up time (high statin users) had a significant 52% lower risk of developing graft loss compared to those on statin therapy $<$50% of the post-transplant follow-up time (low statin users), independent of race (African American *versus* not African American) [123]. High statin use did not influence the incidence of acute rejection, and significantly reduced the risk of death only in African American KTRs.

The results of a recent survival meta-analysis suggest that statin use is associated with improved patient and graft survival after KT [124].

Despite some degree of uncertainty, only statins demonstrated to reduce CV events in at least one large and well-conducted RCT, and therefore we suggest using statins as first-line treatment for lipid lowering. The statin dose should be adjusted according to renal function, as indicated by the KDIGO Clinical Practice Guideline for Lipid Management in CKD [109]. Potential adverse effects such as dysglycaemia [39] should be taken into account, and drug–drug interactions should be considered when selecting and dosing a lipid-lowering agent in patients on immunosuppressive regimens [115].

Evidence supporting the use of ezetimibe, either alone or on top of statin therapy, comes from small, non-controlled studies. Combination of simvastatin 10 mg with ezetimibe 10 mg for 6 months was well tolerated, and resulted in reductions in LDL cholesterol of nearly 50%, with more than half of patients reaching the target LDL level of $<$100 mg/dL in a relatively small, non-randomized trial in Korean KTRs [125]. The results of another small study in which KTRs who were treated with ezetimibe alone or in conjunction with a statin for a mean of 18 $\pm$ 6 months suggest that ezetimibe might be well tolerated and effective in reducing LDL cholesterol in KTRs with hypercholesterolemia [126]. To the best of our knowledge, no outcome data are available for this drug in KTRs.

We could not find any study on proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in KTRs. These monoclonal antibodies provide significant reductions in LDL cholesterol levels and CV events [127], are unlikely to interact with other drugs [128] and might be a promising therapeutic option in patients with reduced renal function, although data are lacking in patients with more severe impairments [129].

1 We suggest that all patient should receive healthy lifestyle advice (*Not Graded*)
2 In adult kidney transplant recipients, we suggest treatment with a statin as first line (2ØØØO).
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*)

Obesity

Weight gain after transplantation is very common, occurring in up to 50% of KTRs [130,131], mainly in the first year after KT [132] and due to abdominal accumulation of body fat mass [89,133,134]. Factors contributing to weight gain after KT include corticosteroid therapy, improved appetite due to correction of uraemia and elimination of dietary restrictions [132]. Obesity is strongly associated with reduced long-term patient- and graft survival [135–137], with the risks for adverse outcome progressively increasing with increasing body mass index (BMI) [138]. Therefore, weight reduction in obese KTRs may provide beneficial effects on graft and patient survival.

Given the impact of obesity on patient and graft survival in KTRs [139], we suggest screening KTRs for obesity at each visit, by measuring height and weight to calculate BMI. In the general population abdominal obesity, as evidenced by increased waist circumference, has been associated with increased CVD risk more strongly than BMI [140,141]. There is evidence that waist circumference is associated with increased mortality after adjustment for BMI in KTRs, whereas higher BMI was associated with lower mortality after adjustment for waist circumference [142]. These data suggest that waist circumference may better predict long-term survival in KTRs, and we suggest measuring waist circumference in when weight and physical appearance suggest obesity, but BMI is $<$ 30 kg/m^2.

Only one small randomized trial evaluated the effect of dietary advice *versus* standard care in KTRs (normal weight, overweight and obese) [143]. However, in this study no significant changes in weight or weight circumference were observed during follow-up. Total cholesterol, LDL cholesterol and triglycerides declined only in the

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intervention group. In a very small study that assessed the effect of an intensive lifestyle intervention comprising physical exercise, behavioural interventions and nutritional guidance in obese KTRs, after 12 months the intervention group was weight-stable and had improvements in body composition (greater lean mass), whereas the BMI of patients in the control group increased on average from 38 to 46 kg/m^2 [144].

Trials assessing the effect of lifestyle interventions on the prevention of weight gain after KT are currently ongoing [102,145].

In the absence of high quality studies on the effect of lifestyle interventions in obese KTRs, and taking into account the evidence for the benefit of providing lifestyle interventions for the treatment of obesity in the general population, it is reasonable to follow the lifestyle recommendations issued for the general population [19,22].

Bariatric surgery has been shown to be superior to nonsurgical obesity management in reducing all-cause mortality in the general population with obesity [146]. Indications to bariatric surgery include class III obesity (BMI $\geq$ 40 kg/m^2) or class II obesity (BMI 35–40 kg/m^2) with comorbidities in which surgically induced weight loss is expected to improve the disorder [147]. In recent years, given the metabolic benefits associated with bariatric surgery in patients with diabetes, it has been recognized that metabolic surgery should also be considered as an option to treat type 2 diabetes in patients with class I obesity (BMI 30.0–34.9 kg/m^2) and inadequately controlled hyperglycaemia despite optimal medical treatment [148].

Several small case series have reported the outcomes of bariatric surgery (either Roux-en-Y gastric bypass [RYGB] or laparoscopic vertical sleeve gastrectomy [LVSG]) in KTRs [149]. Excess weight loss ranged from 31 to 61% in these series, and mortality rates were equal to those among patients on the waiting list. Overall, RYGB and LVSG showed comparable results with low mortality and complication rates. However, in the long term, RYGB may increase the risk of hyperoxaluria and nephrocalcinosis [150], and possibly the risk of acute rejection by reducing drug exposure [151] in KTRs. A comparison between morbidly obese KTRs treated with bariatric surgery or standard lifestyle recommendations after KT found that patients treated with bariatric surgery had significantly lower BMI at 6 months after KT, and significantly more patients had slow and delayed graft function in the lifestyle group [152]. No differences in metabolic and safety outcomes were detected. More recently, a retrospective study compared KTRs who underwent bariatric surgery with controls matched for age, sex, and time elapsed since transplantation [153]. Mean follow-up was 2.4 years. Improvements in renal function, graft survival, and obesity-related co-morbidities were found in KTRs who underwent bariatric surgery *versus* controls. No major effects of bariatric surgery on the absorption of immunosuppressive drugs have been described. Based on the available evidence, bariatric surgery in KTRs appears to be effective for weight loss and associated with low rates of complications and mortality. No long-term studies are available that assessed the effect of bariatric surgery o CV outcomes. We suggest that 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.

1 We suggest assessing obesity at each visit (Not Graded). Measure height and weight at each visit to calculate BMI (2ØØØO). Measure waist circumference when weight and physical appearance suggest obesity, but BMI is $<$ 30 kg/m^2 (2ØØOO).
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 (2ØØOO).

BMI, body mass index; KTRs, kidney transplant recipients.

Conclusions

Post-transplantation diabetes mellitus, dyslipidaemias and overweight/obesity are common metabolic disturbances among KTRs that may undermine graft and/or recipient outcomes [7–9]. Increasing awareness among healthcare professionals involved in the management of KTRs is of paramount importance to systematically implement timely and accurate screening for metabolic alterations in KTRs. Early detection allows early implementation of appropriate management strategies, although more research is needed to develop robust recommendations on several aspects in the setting of KT, including glycaemic and LDL cholesterol targets in PTDM, choice of glucose and lipid lowering agents, management of overweight/obesity. These aspects should be the focus of future research to fill the gaps in current knowledge. This joint position statement is based on currently available evidence on the prevention, diagnosis and treatment of metabolic alterations in KTRs and will support healthcare professionals in the decision-making process in this context. The choice of treatment should be individualised and based on several factors, such as the expected risk/benefit ratio for the individual patient, her/his preferences, and the availability of healthcare resources.

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References

[1] Italian Ministry of Health. National Italian transplant centre. Italian and European data. Available at:http://www.trapianti.salute.gov.it/trapianti/archivioDatiCnt.jsp Last, . [Accessed 28 February 2020].

[2] McAdams-DeMarco MA, James N, Salter ML, Walston J, Segev DL. Trends in kidney transplant outcomes in older adults. J Am Geriatr Soc 2014;62:2235–42.

[3] Conte C, Secchi A. Post-transplantation diabetes in kidney transplant recipients: an update on management and prevention. Acta Diabetol 2018;55:763–79.

[4] Sharif A, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant 2014;14:1992–2000.

[5] Jenssen T, Hartmann A. Post-transplant diabetes mellitus in patients with solid organ transplants. Nat Rev Endocrinol 2019;15:172–88.

[6] Schaenman J, Liao D, Phonphok K, Bunnapradist S, Karlamangla A. Predictors of early a nd late mortality in older kidney transplant recipients. Transplant Proc 2019;51:684–91.

[7] Erturk T, Berber I, Cakir U. Effect of obesity on clinical outcomes of kidney transplant patients. Transplant Proc 2019;51:1093–5.

[8] Hill CJ, Courtney AE, Cardwell CR, Maxwell AP, Lucarelli G, Veroux M, et al. Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis. Nephrol Dial Transplant 2015;30:1403–11.

[9] Pontremoli R, Bellizzi V, Bianchi S, Bigazzi R, Cernaro V, Del Vecchio L, et al. Management of dyslipidaemia in patients with chronic kidney disease: a position paper endorsed by the Italian Society of Nephrology. J Nephrol 2020.

[10] Kidney Disease: Improving Global Outcomes Transplant Work G. KDIGO clinical practice guideline for the care of kidney transplant recipients. Am J Transplant 2009;9(Suppl 3):S1–155.

[11] American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2019. Diabetes Care 2019;42:S13–28.

[12] American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2019. Diabetes Care 2019;42:S61–70.

[13] American Diabetes Association. 10. Cardiovascular disease and risk management: standards of medical care in diabetes-2019. Diabetes Care 2019;42:S103–23.

[14] American Diabetes Association. 15. Diabetes care in the hospital: standards of medical care in diabetes-2019. Diabetes Care 2019;42:S173–81.

[15] Chadban S, Chan M, Fry K, Patwardhan A, Ryan C, Trevillian P, et al. The CARI guidelines. Nutritional management of diabetes mellitus in adult kidney transplant recipients. Nephrology 2010;15(Suppl 1):S37–9.

[16] Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2019.

[17] Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. Diabetes Care 2019;42:731–54.

[18] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American heart association task force on clinical practice guidelines. Circulation 2019;139:e1082–143.

[19] Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American heart association task force on practice guidelines and the obesity society. Circulation 2014;129:S102–38.

[20] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2019;41(1):111–88. https://doi.org/10.1093/eurheartj/ehz455.

[21] Wanner C, Tonelli M. Kidney disease: improving global outcomes lipid guideline development work group M. KDIGO clinical practice guideline for lipid management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85:1303–9.

[22] Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, et al. European guidelines for obesity management in adults. Obes Facts 2015;8:402–24.

[23] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

[24] Chakkera HA, Weil EJ, Castro J, Heilman RL, Reddy KS, Mazur MJ, et al. Hyperglycemia during the immediate period after kidney transplantation. Clin J Am Soc Nephrol 2009;4:853–9.

[25] Aouad LJ, Clayton P, Wyburn KR, Gracey DM, Chadban SJ. Evolution of glycemic control and variability after kidney transplant. Transplantation 2018;102:1563–8.

[26] Yates CJ, Fourlanos S, Colman PG, Cohney SJ. Screening for new-onset diabetes after kidney transplantation: limitations of fasting glucose and advantages of afternoon glucose and glycated hemoglobin. Transplantation 2013;96:726–31.

[27] Chakkera HA, Knowler WC, Devarapalli Y, Weil EJ, Heilman RL, Dueck A, et al. Relationship between inpatient hyperglycemia and insulin treatment after kidney transplantation and future new onset diabetes mellitus. Clin J Am Soc Nephrol 2010;5:1669–75.

[28] Rodrigo E, Santos L, Pinera C, Quintanar JA, Ruiz JC, Fernandez-Fresnedo G, et al. Early prediction of new-onset diabetes mellitus by fifth-day fasting plasma glucose, pulse pressure, and proteinuria. Transplant Proc 2011;43:2208–10.

[29] Pimentel AL, Cavagnolli G, Camargo JL. Diagnostic accuracy of glycated hemoglobin for post-transplantation diabetes mellitus after kidney transplantation: systematic review and meta-analysis. Nephrol Dial Transplant 2017;32:565–72.

[30] Valderhaug TG, Jenssen T, Hartmann A, Midtvedt K, Holdaas H, Reisaeter AV, et al. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. Transplantation 2009;88:429–34.

[31] Eide IA, Halden TA, Hartmann A, Asberg A, Dahle DO, Reisaeter AV, et al. Mortality risk in post-transplantation diabetes mellitus based on glucose and HbA1c diagnostic criteria. Transpl Int 2016;29:568–78.

[32] Ussif AM, Asberg A, Halden TAS, Nordheim E, Hartmann A, Jenssen T. Validation of diagnostic utility of fasting plasma glucose and HbA1c in stable renal transplant recipients one year after transplantation. BMC Nephrol 2019;20:12.

[33] Ali IH, Adberrahim E, Ben Abdelghani K, Barbouch S, McHirgui N, Khiari K, et al. Incidence and risk factors for post-renal transplant diabetes mellitus. Transplant Proc 2011;43:568–71.

[34] Bayes B, Granada ML, Pastor MC, Lauzurica R, Salinas I, Sanmarti A, et al. Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. Am J Transplant 2007;7:416–22.

[35] Cullen TJ, McCarthy MP, Lasarev MR, Barry JM, Stadler DD. Body mass index and the development of new-onset diabetes mellitus or the worsening of pre-existing diabetes mellitus in adult kidney transplant patients. J Ren Nutr 2014;24:116–22.

[36] Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 2003;3:178–85.

[37] Parikh CR, Klem P, Wong C, Yalavarthy R, Chan L. Obesity as an independent predictor of posttransplant diabetes mellitus. Transplant Proc 2003;35:2922–6.

[38] Guthoff M, Wagner R, Weichbrodt K, Nadalin S, Konigsrainer A, Haring HU, et al. Dynamics of glucose metabolism after kidney transplantation. Kidney Blood Press Res 2017;42:598–607.

[39] Choe EY, Wang HJ, Kwon O, Cho Y, Huh KH, Kim MS, et al. HMG CoA reductase inhibitor treatment induces dysglycemia in renal allograft recipients. Transplantation 2014;97:419–25.

[40] Suszynski TM, Gillingham KJ, Rizzari MD, Dunn TB, Payne WD, Chinnakotla S, et al. Prospective randomized trial of maintenance immunosuppression with rapid discontinuation of prednisone in adult kidney transplantation. Am J Transplant 2013;13:961–70.

[41] Batista F, Auyanet I, Torregrosa JV, Oppenheimer F. Long-term follow-up after conversion from tacrolimus to cyclosporin in renal transplant patients with new-onset diabetes mellitus after transplantation. Transplant Proc 2012;44:2582–4.

[42] Wissing KM, Abramowicz D, Weekers L, Budde K, Rath T, Witzke O, et al. Prospective randomized study of conversion from

Please cite this article as: Conte C et al., Management of metabolic alterations in adult kidney transplant recipients: A joint position statement of the Italian Society of Nephrology (SIN), the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID), Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2020.05.004

tacrolimus to cyclosporine A to improve glucose metabolism in patients with posttransplant diabetes mellitus after renal transplantation. Am J Transplant 2018;18:1726–34.
[43] Sommerer C, Witzke O, Lehner F, Arns W, Reinke P, Eisenberger U, et al. Onset and progression of diabetes in kidney transplant patients receiving everolimus or cyclosporine therapy: an analysis of two randomized, multicenter trials. BMC Nephrol 2018;19:237.
[44] Veroux M, Tallarita T, Corona D, Sinagra N, Giaquinta A, Zerbo D, et al. Conversion to sirolimus therapy in kidney transplant recipients with new onset diabetes mellitus after transplantation. Clin Dev Immunol 2013;2013:496974.
[45] Nanmoku K, Shinzato T, Kubo T, Shimizu T, Kimura T, Yagisawa T. Steroid withdrawal using everolimus in ABO-incompatible kidney transplant recipients with post-transplant diabetes mellitus. Transplant Proc 2018;50:1050–5.
[46] Nanmoku K, Kurosawa A, Kubo T, Shinzato T, Shimizu T, Kimura T, et al. Conversion from steroid to everolimus in maintenance kidney transplant recipients with posttransplant diabetes mellitus. Exp Clin Transplant 2019;17:47–51.
[47] Rizzari MD, Suszynski TM, Gillingham KJ, Dunn TB, Ibrahim HN, Payne WD, et al. Ten-year outcome after rapid discontinuation of prednisone in adult primary kidney transplantation. Clin J Am Soc Nephrol 2012;7:494–503.
[48] Haller MC, Royuela A, Nagler EV, Pascual J, Webster AC. Steroid avoidance or withdrawal for kidney transplant recipients. Cochrane Database Syst Rev 2016:CD005632.
[49] Desai VCA, Ferrand Y, Cavanaugh TM, Kelton CML, Caro JJ, Goebel J, et al. Comparative effectiveness of tacrolimus-based steroid sparing versus steroid maintenance regimens in kidney transplantation: results from discrete event simulation. Med Decis Making 2017;37:827–43.
[50] Mourad G, Glyda M, Albano L, Viklicky O, Merville P, Tyden G, et al. Incidence of posttransplantation diabetes mellitus in De Novo kidney transplant recipients receiving prolonged-release tacrolimus-based immunosuppression with 2 different corticosteroid minimization strategies: ADVANCE, A randomized controlled trial. Transplantation 2017;101:1924–34.
[51] Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65.
[52] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–53.
[53] Fullerton B, Jeitler K, Seitz M, Horvath K, Berghold A, Siebenhofer A. Intensive glucose control versus conventional glucose control for type 1 diabetes mellitus. Cochrane Database Syst Rev 2014:CD009122.
[54] Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract 1995;28:103–17.
[55] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, Lachin JM, White NH, Hainsworth DP, Sun W, Cleary PA, et al. Effect of intensive diabetes therapy on the progression of diabetic retinopathy in patients with type 1 diabetes: 18 years of follow-up in the DCCT/EDIC. Diabetes 2015;64:631–42.
[56] Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group, Lachin JM, Genuth S, Cleary P, Davis MD, Nathan DM. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. N Engl J Med 2000;342:381–9.
[57] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89.
[58] Turnbull FM, Abraira C, Anderson RJ, Byington RP, Chalmers JP, Duckworth WC, et al. Intensive glucose control and macrovascular outcomes in type 2 diabetes. Diabetologia 2009;52:2288–98.
[59] Nathan DM, Zinman B, Cleary PA, Backlund JY, Genuth S, Miller R, et al., Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: the diabetes control and complications trial/epidemiology of diabetes interventions and complications and Pittsburgh epidemiology of diabetes complications experience (1983-2005). Arch Intern Med 2009;169:1307–16.
[60] Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–53.
[61] Kim YC, Shin N, Lee S, Hyuk H, Kim YH, Kim H, et al. Effect of post-transplant glycemic control on long-term clinical outcomes in kidney transplant recipients with diabetic nephropathy: a multicenter cohort study in Korea. PloS One 2018;13:e0195566.
[62] Lam NN, Kim SJ, Knoll GA, McArthur E, Lentine KL, Naylor KL, et al. The risk of cardiovascular disease is not increasing over time despite aging and higher comorbidity burden of kidney transplant recipients. Transplantation 2017;101:588–96.
[63] Maldonado F, Tapia G, Ardiles L. Early hyperglycemia: a risk factor for posttransplant diabetes mellitus among renal transplant recipients. Transplant Proc 2009;41:2664–7.
[64] Memon SS, Tandon N, Mahajan S, Bansal VK, Krishna A, Subbiah A. The prevalence of new onset diabetes mellitus after renal transplantation in patients with immediate posttransplant hyperglycemia in a tertiary care centre. Indian J Endocrinol Metab 2017;21:871–5.
[65] Wojtusciszyn A, Mourad G, Bringer J, Renard E. Continuous glucose monitoring after kidney transplantation in non-diabetic patients: early hyperglycaemia is frequent and may herald post-transplantation diabetes mellitus and graft failure. Diabetes Metab 2013;39:404–10.
[66] Kek PC, Tan HC, Kee TY, Goh SY, Bee YM. Day 1 post-operative fasting hyperglycemia may affect graft survival in kidney transplantation. Ann Transplant 2013;18:265–72.
[67] Lansang MC, Umpierrez GE. Inpatient hyperglycemia management: a practical review for primary medical and surgical teams. Cleve Clin J Med 2016;83:S34–43.
[68] Werzowa JM, Saemann MD, Mohl A, Bergmann M, Kaltenecker CC, Brozek W, et al. A randomized controlled trial-based algorithm for insulin-pump therapy in hyperglycemic patients early after kidney transplantation. PloS One 2018;13:e0193569.
[69] Hermayer KL, Egidi MF, Finch NJ, Baliga P, Lin A, Kettinger L, et al. A randomized controlled trial to evaluate the effect of glycemic control on renal transplantation outcomes. J Clin Endocrinol Metab 2012;97:4399–406.
[70] Hecking M, Haidinger M, Doller D, Werzowa J, Tura A, Zhang J, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. J Am Soc Nephrol 2012;23:739–49.
[71] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). Diabetologia 2018;61:2461–98.
[72] European Medicines Agency. Use of metformin to treat diabetes now expanded to patients with moderately reduced kidney function. Available at:http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Metformin_31/WC500214235.pdf, ; 2016.
[73] Guideline development group. Clinical Practice Guideline on management of patients with diabetes and chronic kidney disease stage 3b or higher (eGFR <45 mL/min). Nephrol Dial Transplant 2015;30(Suppl 2):ii1–142.
[74] Piotti G, Gandolfini I, Palmisano A, Maggiore U. Metabolic risk profile in kidney transplant candidates and recipients. Nephrol Dial Transplant 2019;34:388–400.
[75] Stephen J, Anderson-Haag TL, Gustafson S, Snyder JJ, Kasiske BL, Israni AK. Metformin use in kidney transplant recipients in the United States: an observational study. Am J Nephrol 2014;40:546–53.
[76] Alnasrallah B, Pilmore H, Manley P. Protocol for a pilot randomised controlled trial of metformin in pre-diabetes after kidney transplantation: the Transplantation and Diabetes (Transdiab) study. BMJ Open 2017;7:e016813.
[77] Lo C, Jun M, Badve SV, Pilmore H, White SL, Hawley C, et al. Glucose-lowering agents for treating pre-existing and new-onset

Please cite this article as: Conte C et al., Management of metabolic alterations in adult kidney transplant recipients: A joint position statement of the Italian Society of Nephrology (SIN), the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID), Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2020.05.004

diabetes in kidney transplant recipients. Cochrane Database Syst Rev 2017;2:CD009966.
[78] Liou JH, Liu YM, Chen CH. Management of diabetes mellitus with glucagonlike peptide-1 agonist liraglutide in renal transplant recipients: a retrospective study. Transplant Proc 2018;50:2502–5.
[79] Shah M, Virani Z, Rajput P, Shah B. Efficacy and safety of canagliflozin in kidney transplant patients. Indian J Nephrol 2019;29:278–81.
[80] Halden TAS, Kvitne KE, Midtvedt K, Rajakumar L, Robertsen I, Brox J, et al. Efficacy and safety of empagliflozin in renal transplant recipients with posttransplant diabetes mellitus. Diabetes Care 2019;42:1067–74.
[81] Fei Y, Tsoi MF, Cheung BMY. Cardiovascular outcomes in trials of new antidiabetic drug classes: a network meta-analysis. Cardiovasc Diabetol 2019;18:112.
[82] Seidu S, Kunutsor SK, Cos X, Gillani S, Khunti K, For, et al. SGLT2 inhibitors and renal outcomes in type 2 diabetes with or without renal impairment: a systematic review and meta-analysis. Prim Care Diabetes 2018;12:265–83.
[83] Dekkers CCJ, Wheeler DC, Sjostrom CD, Stefansson BV, Cain V, Heerspink HJL. Effects of the sodium-glucose co-transporter 2 inhibitor dapagliflozin in patients with type 2 diabetes and Stages 3b-4 chronic kidney disease. Nephrol Dial Transplant 2018;33:2005–11.
[84] Vanhove T, Remijsen Q, Kuypers D, Gillard P. Drug-drug interactions between immunosuppressants and antidiabetic drugs in the treatment of post-transplant diabetes mellitus. Transplant Rev 2017;31:69–77.
[85] Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, et al., Ascend Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379:1529–39.
[86] Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet 2018;392:387–99.
[87] Scally B, Emberson JR, Spata E, Reith C, Davies K, Halls H, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol 2018;3:231–41.
[88] Painter PL, Topp KS, Krasnoff JB, Adey D, Strasner A, Tomlanovich S, et al. Health-related fitness and quality of life following steroid withdrawal in renal transplant recipients. Kidney Int 2003;63:2309–16.
[89] van den Ham EC, Kooman JP, Christiaans MH, Nieman FH, van Hooff JP. Weight changes after renal transplantation: a comparison between patients on 5-mg maintenance steroid therapy and those on steroid-free immunosuppressive therapy. Transpl Int 2003;16:300–6.
[90] Zelle DM, Kok T, Dontje ML, Danchell EI, Navis G, van Son WJ, et al. The role of diet and physical activity in post-transplant weight gain after renal transplantation. Clin Transplant 2013;27:E484–90.
[91] Zelle DM, Klaassen G, van Adrichem E, Bakker SJ, Corpeleijn E, Navis G. Physical inactivity: a risk factor and target for intervention in renal care. Nat Rev Nephrol 2017;13:152–68.
[92] Zelle DM, Corpeleijn E, Stolk RP, de Greef MH, Gans RO, van der Heide JJ, et al. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. Clin J Am Soc Nephrol 2011;6:898–905.
[93] Orazio L, Hickman I, Armstrong K, Johnson D, Banks M, Isbel N. Higher levels of physical activity are associated with a lower risk of abnormal glucose tolerance in renal transplant recipients. J Ren Nutr 2009;19:304–13.
[94] Didsbury M, McGee RG, Tong A, Craig JC, Chapman JR, Chadban S, et al. Exercise training in solid organ transplant recipients: a systematic review and meta-analysis. Transplantation 2013;95:679–87.
[95] Greenwood SA, Koufaki P, Mercer TH, Rush R, O'Connor E, Tuffnell R, et al. Aerobic or resistance training and pulse wave velocity in kidney transplant recipients: a 12-week pilot randomized controlled trial (the exercise in renal transplant [ExeRT] trial). Am J Kidney Dis 2015;66:689–98.
[96] O'Connor EM, Koufaki P, Mercer TH, Lindup H, Nugent E, Goldsmith D, et al. Long-term pulse wave velocity outcomes with aerobic and resistance training in kidney transplant recipients - a pilot randomised controlled trial. PloS One 2017;12:e0171063.
[97] Roi GS, Stefoni S, Mosconi G, Brugin E, Burra P, Ermolao A, et al. Physical activity in solid organ transplant recipients: organizational aspects and preliminary results of the Italian project. Transplant Proc 2014;46:2345–9.
[98] Sharif A, Moore R, Baboolal K. Influence of lifestyle modification in renal transplant recipients with postprandial hyperglycemia. Transplantation 2008;85:353–8.
[99] Karelis AD, Hebert MJ, Rabasa-Lhoret R, Rakel A. Impact of resistance training on factors involved in the development of new-onset diabetes after transplantation in renal transplant recipients: an open randomized pilot study. Can J Diabetes 2016;40:382–8.
[100] Lorenz EC, Amer H, Dean PG, Stegall MD, Cosio FG, Cheville AL. Adherence to a pedometer-based physical activity intervention following kidney transplant and impact on metabolic parameters. Clin Transplant 2015;29:560–8.
[101] Gomes-Neto AW, Oste MCJ, Sotomayor CG, VDB E, Geleijnse JM, Gans ROB, et al. Fruit and vegetable intake and risk of post-transplantation diabetes in renal transplant recipients. Diabetes Care 2019;42:1645–52.
[102] Klaassen G, Zelle DM, Navis GJ, Dijkema D, Bemelman FJ, Bakker SJL, et al. Lifestyle intervention to improve quality of life and prevent weight gain after renal transplantation: Design of the Active Care after Transplantation (ACT) randomized controlled trial. BMC Nephrol 2017;18:296.
[103] Methven S, Steenkamp R, Fraser S. UK renal registry 19th annual report: chapter 5 survival and causes of death in UK adult patients on renal replacement therapy in 2015: national and centre-specific analyses. Nephron 2017;137(Suppl 1):117–50.
[104] Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US renal data system 2017 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2018;71:A7.
[105] Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32:S112–9.
[106] Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. Am J Kidney Dis 2000;35:S117–31.
[107] Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725–30.
[108] Warden BA, Duell PB. Management of dyslipidemia in adult solid organ transplant recipients. J Clin Lipidol 2019;13:231–45.
[109] Tonelli M, Wanner C, Kidney Disease. Improving global outcomes lipid guideline development work group M. Lipid management in chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2013 clinical practice guideline. Ann Intern Med 2014;160:182.
[110] Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet 2003;361:2024–31.
[111] Norby GE, Holme I, Fellstrom B, Jardine A, Cole E, Abedini S, et al. Effect of fluvastatin on cardiac outcomes in kidney transplant patients with systemic lupus erythematosus: a randomized placebo-controlled study. Arthritis Rheum 2009;60:1060–4.
[112] Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. Ann Intern Med 2012;157:263–75.
[113] Palmer SC, Navaneethan SD, Craig JC, Perkovic V, Johnson DW, Nigwekar SU, et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev 2014:CD005019.
[114] Yazbek DC, de Carvalho AB, Barros CS, Medina Pestana JO, Canziani ME. Effect of statins on the progression of coronary calcification in kidney transplant recipients. PloS One 2016;11:e0151797.
[115] Wiggins BS, Saseen JJ, Page 2nd RL, Reed BN, Sneed K, Kostis JB, et al. Recommendations for management of

Please cite this article as: Conte C et al., Management of metabolic alterations in adult kidney transplant recipients: A joint position statement of the Italian Society of Nephrology (SIN), the Italian Society for Organ Transplantation (SITO) and the Italian Diabetes Society (SID), Nutrition, Metabolism & Cardiovascular Diseases, https://doi.org/10.1016/j.numecd.2020.05.004

clinically significant drug-drug interactions with statins and select agents used in patients with cardiovascular disease: a scientific statement from the American heart association. Circulation 2016;134:e468–95.
[116] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267–78.
[117] Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med 2009;360:1395–407.
[118] Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353:238–48.
[119] Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181–92.
[120] Cholesterol Treatment Trialists' (CTT) Collaboration, Herrington WG, Emberson J, Mihaylova B, Blackwell L, Reith C, et al. Impact of renal function on the effects of LDL cholesterol lowering with statin-based regimens: a meta-analysis of individual participant data from 28 randomised trials. Lancet Diabetes Endocrinol 2016;4:829–39.
[121] Soveri I, Abedini S, Holdaas H, Jardine A, Eriksson N, Fellstrom B. Metabolic syndrome and cardiovascular risk in renal transplant recipients: effects of statin treatment. Clin Transplant 2009;23:914–20.
[122] Messow CM, Isles C. Meta-analysis of statins in chronic kidney disease: who benefits? QJM 2017;110:493–500.
[123] Ozieh MN, Taber DJ, Egede LE. Does african American race impact statin efficacy in renal transplant outcomes? Medicine (Baltim) 2015;94:e2283.
[124] Rostami Z, Moteshaker Arani M, Salesi M, Safiabadi M, Einollahi B. Effect of statins on patients and graft survival in kidney transplant recipients: a survival meta-analysis. Iran J Kidney Dis 2017;11:329–38.
[125] Yoon HE, Song JC, Hyoung BJ, Hwang HS, Lee SY, Jeon YJ, et al. The efficacy and safety of ezetimibe and low-dose simvastatin as a primary treatment for dyslipidemia in renal transplant recipients. Korean J Intern Med 2009;24:233–7.
[126] Savvidaki E, Koukoulaki M, Benou A, Roumeliotou M, Fourtounas C, Kalliakmani P, et al. Ezetimibe is effective in the treatment of persistent hyperlipidemia of renal allograft recipients. Clin Nephrol 2011;75:107–12.
[127] Schmidt AF, Pearce LS, Wilkins JT, Overington JP, Hingorani AD, Casas JP. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2017;4:CD011748.
[128] Ferri N, Bellosta S, Baldessin L, Boccia D, Racagni G, Corsini A. Pharmacokinetics interactions of monoclonal antibodies. Pharmacol Res 2016;111:592–9.
[129] Mafham M, Haynes R. PCSK9 inhibition: ready for prime time in CKD? Kidney Int 2018;93:1267–9.
[130] Baum CL. Weight gain and cardiovascular risk after organ transplantation. JPEN - J Parenter Enter Nutr 2001;25:114–9.
[131] Johnson CP, Gallagher-Lepak S, Zhu YR, Porth C, Kelber S, Roza AM, et al. Factors influencing weight gain after renal transplantation. Transplantation 1993;56:822–7.
[132] Chan W, Bosch JA, Jones D, McTernan PG, Phillips AC, Borrows R. Obesity in kidney transplantation. J Ren Nutr 2014;24:1–12.
[133] Pantik C, Cho YE, Hathaway D, Tolley E, Cashion A. Characterization of body composition and fat mass Distribution 1 Year after kidney transplantation. Prog Transplant 2017;27:10–5.
[134] Workeneh B, Moore LW, Nolte Fong JV, Shypailo R, Gaber AO, Mitch WE. Successful kidney transplantation is associated with weight gain from truncal obesity and insulin resistance. J Ren Nutr 2019.
[135] Gore JL, Pham PT, Danovitch GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and outcome following renal transplantation. Am J Transplant 2006;6:357–63.
[136] Hoogeveen EK, Aalten J, Rothman KJ, Roodnat JI, Mallat MJ, Borm G, et al. Effect of obesity on the outcome of kidney transplantation: a 20-year follow-up. Transplantation 2011;91:869–74.
[137] Sancho A, Avila A, Gavela E, Beltran S, Fernandez-Najera JE, Molina P, et al. Effect of overweight on kidney transplantation outcome. Transplant Proc 2007;39:2202–4.
[138] Kwan JM, Hajjiri Z, Metwally A, Finn PW, Perkins DL. Effect of the obesity epidemic on kidney transplantation: obesity is independent of diabetes as a risk factor for adverse renal transplant outcomes. PloS One 2016;11:e0165712.
[139] Glicklich D, Mustafa MR. Obesity in kidney transplantation: impact on transplant candidates, recipients, and Donors. Cardiol Rev 2019;27:63–72.
[140] Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. Am Heart J 2005;149:54–60.
[141] Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008;359:2105–20.
[142] Kovesdy CP, Czira ME, Rudas A, Ujszaszi A, Rosivall L, Novak M, et al. Body mass index, waist circumference and mortality in kidney transplant recipients. Am J Transplant 2010;10:2644–51.
[143] Orazio LK, Isbel NM, Armstrong KA, Tarnarskyj J, Johnson DW, Hale RE, et al. Evaluation of dietetic advice for modification of cardiovascular disease risk factors in renal transplant recipients. J Ren Nutr 2011;21:462–71.
[144] Tzvetanov I, West-Thielke P, D'Amico G, Johnsen M, Ladik A, Hachaj G, et al. A novel and personalized rehabilitation program for obese kidney transplant recipients. Transplant Proc 2014;46:3431–7.
[145] Pedrollo EF, Nicoletto BB, Carpes LS, de Freitas JMC, Buboltz JR, Forte CC, et al. Effect of an intensive nutrition intervention of a high protein and low glycemic-index diet on weight of kidney transplant recipients: study protocol for a randomized clinical trial. Trials 2017;18:413.
[146] Reges O, Greenland P, Dicker D, Leibowitz M, Hoshen M, Gofer I, et al. Association of bariatric surgery using laparoscopic banding, roux-en-Y gastric bypass, or laparoscopic sleeve gastrectomy vs usual care obesity management with all-cause mortality. J Am Med Assoc 2018;319:279–90.
[147] Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres AJ, Weiner R, et al. Interdisciplinary European Guidelines on metabolic and bariatric surgery. Obes Facts 2013;6:449–68.
[148] Rubino F, Nathan DM, Eckel RH, Schauer PR, Alberti KG, Zimmet PZ, et al. Metabolic surgery in the treatment algorithm for type 2 diabetes: a joint statement by international diabetes organizations. Diabetes Care 2016;39:861–77.
[149] Dziodzio T, Biebl M, Ollinger R, Pratschke J, Denecke C. The role of bariatric surgery in abdominal organ transplantation-the next big challenge? Obes Surg 2017;27:2696–706.
[150] Troxell ML, Houghton DC, Hawkey M, Batiuk TD, Bennett WM. Enteric oxalate nephropathy in the renal allograft: an underrecognized complication of bariatric surgery. Am J Transplant 2013;13:501–9.
[151] Thomas IA, Gaynor JJ, Joseph T, De La Cruz-Munoz N, Sageshima J, Kupin W, et al. Roux-en-Y gastric bypass is an effective bridge to kidney transplantation: results from a single center. Clin Transplant 2018;32:e13232.
[152] Gheith O, Al-Otaibi T, Halim MA, Mahmoud T, Mosaad A, Yagan J, et al. Bariatric surgery in renal transplant patients. Exp Clin Transplant 2017;15:164–9.
[153] Schindel H, Winkler J, Yemini R, Carmeli I, Nesher E, Keidar A. Survival benefit in bariatric surgery kidney recipients may be mediated through effects on kidney graft function and improvement of co-morbidities: a case-control study. Surg Obes Relat Dis 2019;15:621–7.

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