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REVIEW

Transplant options for patients with type 2 diabetes and chronic kidney disease

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Abstract

Chronic kidney disease (CKD) has become a real epidemic around the world, mainly due to ageing and diabetic nephropathy. Although diabetic nephropathy due to type 1 diabetes mellitus (T1DM) has been studied more extensively, the vast majority of the diabetic CKD patients suffer from type 2 diabetes mellitus (T2DM). Renal transplantation has been established as a first line treatment for diabetic nephropathy unless there are major contraindications and provides not only a better quality of life, but also a significant survival advantage over dialysis. However, T2DM patients are less likely to be referred for renal transplantation as they are usually older, obese and present significant comorbidities. As pre-emptive renal transplantation presents a clear survival advantage over dialysis, all T2DM patients with CKD should be referred for early evaluation by a transplant center. The transplant center should have enough time in order to examine their eligibility focusing on special issues related with diabetic nephropathy and explore the best options for each patient. Living donor kidney transplantation should always be considered as the first line treatment. Otherwise, the patient should be listed for deceased donor kidney transplantation. Recent progress in transplantation medicine has improved the "transplant menu" for T2DM patients with diabetic nephropathy and there is an ongoing discussion about the place of simultaneous pancreas kidney (SPK) transplantation in well selected patients. The initial hesitations about the different pathophysiology of T2DM have been forgotten due to the almost similar short- and long-term results with T1DM patients. However, there is still a long way and a lot of ethical and logistical issues before establishing SPK transplantation as an ordinary treatment for T2DM patients. In addition recent advances in bariatric surgery may offer new options for severely obese T2DM patients with CKD. Nevertheless, the existing data for T2DM patients with advanced CKD are rather scarce and bariatric surgery should not be considered as a cure for diabetic nephropathy, but only as a bridge for renal transplantation.

Key words: Bariatric surgery; Cardiovascular complications; Diabetes; Renal transplantation; Pancreas transplantation

Core tip: Kidney transplantation has been established as a first line treatment for patients with type 2 diabetes mellitus (T2DM) and diabetic nephropathy, as it is accompanied with a significant survival advantage over dialysis. Pre-emptive living donor kidney transplantation should be the ultimate goal unless there are obvious contraindications and all patients should be referred for early evaluation by a transplant center. There is an ongoing debate about the exact role of simultaneous pancreas kidney transplantation. At the moment it should be offered only in well selected T2DM patients. Bariatric surgery may serve as a bridge for renal transplantation for severely obese T2DM patients with chronic kidney disease.

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INTRODUCTION

Chronic kidney disease (CKD) has become a real epidemic around the world, mainly due to ageing and diabetic nephropathy[1-3]. Although diabetic nephropathy due to type 1 diabetes mellitus (T1DM) has been studied more extensively, the vast majority (90%-95%) of the diabetic CKD patients suffer from type 2 diabetes mellitus (T2DM). Currently, about 40%-45% of the dialysis (hemodialysis or peritoneal dialysis) population is diabetics and present increased morbidity and mortality compared with other causes of CKD[1-6]. In addition diabetic patients comprise almost 40% of the transplant waiting lists nowadays[7].

Diabetic CKD patients undergoing dialysis present excessive morbidity and mortality mainly due to cardiovascular complications[3-6]. Several years ago, diabetic nephropathy was considered as a relative or absolute contraindication for renal transplantation, due to increased rates of cardiovascular and infectious complications and unacceptable morbidity and mortality. However, the landmark study of Wolfe *et al*[8] has shown that renal transplantation provided a clear survival advantage for diabetics with end-stage renal disease (ESRD) and reduced mortality by 73% compared with patients remaining on the waiting list. The projected life expectancy was more pronounced for younger diabetics (presumably T1DM) reaching a gain of 17 years, whereas the gain was also significant even for patients older than 60 years (presumably T2DM).

Pancreas transplantation and especially simultaneous pancreas kidney (SPK) transplantation outcomes have seen a dramatic improvement regarding both allograft and patient survival, mainly due to advances in immunosuppression and surgical techniques[9-12]. Historically, pancreas transplantation was considered as a relative if not absolute contraindication for T2DM[7] but current data provide evidence that it can also be offered to well selected T2DM patients with CKD with comparable outcomes[7,12-14]. So, the transplant menu for T2DM patients has been expanded, but the best transplant option is still uncertain[15].

This is an update regarding current trends in transplant medicine for T2DM patients with CKD and is based on the studies published in details in peer-reviewed journals, several previous review articles[4-7,16-18] and novel data[14,19-21] which may change our attitudes and policies regarding the management of this frail CKD population.

PRE-TRANSPLANT EVALUATION

There is hard evidence that pre-emptive renal transplantation presents a clear survival advantage over dialysis and all T2DM patients with CKD should be referred for early evaluation by a transplant center[6]. The goal of the pre-transplant risk evaluation is to determine whether the T2DM candidate is eligible for transplantation and discuss all the potential transplant options which may include: (1) kidney transplantation. The kidney allograft may origin from a deceased donor (DDKT) or by a living donor (LDKT). If the operation takes place before the need of dialysis it is referred as pre-emptive KT[22]; (2) simultaneous pancreas kidney (SPK) transplantation, where there is a combined transplantation of both organs, coming usually from the same donor, during a single operation. The origin of the grafts is usually from deceased donors, but there are also reports of segmental pancreatic grafts from living donors[23].

The pros and the cons of both options will be discussed in details below in separate sections of this review.

The contraindications include the general contraindications for any organ transplantation, such as the presence of malignancy, active infection, psychiatric disease, drug/alcohol dependence, morbid obesity and untreated or end-stage organ damage with special emphasis on cardiovascular comorbidities[24,25]. Age should not be considered as an absolute contraindication for renal transplantation[8] but the increased rates of medical and surgical complications and the lower graft survival rates[5,6,8,25], should be clearly explained in elderly diabetic candidates although some other studies did not confirm these results. Most transplant centers do not accept diabetic patients older than 45-50 years for SPK[13,15] although there are reports of SPK transplantation in patients over this limit. In 2010 the international pancreas transplant registry (IPTR) reported that 2% of pancreas transplant recipients were older than 60 years at the time of transplantation[12].

Obesity [body mass index (BMI) > 30-35 kg/m^2] has also been considered as a relative contraindication for transplantation in diabetic patients as it is accompanied with inferior outcomes for both KT[26,27] and SPK[28] mainly due to surgical complications. However, only morbid obesity (BMI > 40 kg/m^2) should be considered as an absolute contraindication. Recent advances in bariatric surgery can ameliorate this contraindication and make even obese T2DM patients eligible for transplantation[29,30]. This important issue will be discussed in the end of this review.

As T2DM patients with diabetic nephropathy present increased cardiovascular morbidity and mortality, the pre-transplant evaluation should focus on the presence and the severity of coronary and peripheral artery disease. Although, there is no consensus regarding the optimal protocol for cardiovascular risk stratification, most transplant centers refer the candidates for cardiac stress testing and/or coronary angiography, especially in ages older than 55-60 years as well as dyslipidemia, history of smoking and presence of cerebrovascular or peripheral vascular disease[6,24]. However, the provocative study of Patel *et al*[31] has challenged this approach reporting that aggressive pre-transplant testing and coronary interventions did not translate into better outcomes post transplantation in high risk patients.

Peripheral arterial occlusive disease and carotid arteries stenosis examination by ultrasound examination are also mandatory in the pre-transplant evaluation. Many centers suggest a more thorough examination in high risk patients by CT or MR angiography or even intra-arterial angiography[6,24].

All possible advantages of transplantation should be

carefully balanced against the potential complications of the surgical procedure and the long-term side-effects of immunosuppression[15]. A state of the art approach is to refer the patient with advanced diabetic nephropathy to the transplant center early, when his estimated glomerular filtration rate is about 25-30 mL/min in order to provide enough time for evaluation of both the transplant candidate and any potential living donors[6]. However, most T2DM patients with CKD are not referred early even to a nephrologist and the above policy remains rather elusive. Nevertheless, by an early referral, the transplant team can evaluate more thoroughly the diabetic candidate and order more complicated investigations such as coronary angiography, without increasing the risk of premature start of dialysis[6]. In addition, early referral will also provide time to search for LDKT with the most suitable donor or even alternative options for pre-emptive transplantation in cases of immunologically incompatible but still qualified donors, such as kidney paired donation[32].

As SPK transplantation may also be an option for selected T2DM patients with CKD, all available data should be discussed with the transplant candidate. It should be emphasized that SPK transplantation is surgically more challenging compared with kidney transplantation, is accompanied with increased rates of complications and the short- and long-term outcomes should be reported in an unbiased way. However, it is not a standard procedure for most transplant centers and the patient may need to be referred to a more experienced center.

Regarding T2DM patients eligible for transplantation the United Network for Organ Sharing (UNOS) has defined the following criteria for SPK: (1) insulin therapy and C-peptide level < 2 ng/mL; or (2) insulin therapy with C-peptide level > 2 ng/mL and BMI < 28 kg/m^2[13,14,19,33]. The initial concern regarding pancreas transplantation in T2DM patients was insulin resistance that prevails in this type of DM and may result in lower pancreas allograft survival due to β cell exhaustion from the increased insulin demands[15,21]. These concerns and the discussion about the pros and the cons of SPK transplantation are discussed later in this review.

KIDNEY TRANSPLANTATION FOR T2DM PATIENTS WITH CKD

Kidney transplantation is not a "panacea" for T2DM patients with CKD. Although pre-emptive renal transplantation[34], offers a significant survival advantage for all (diabetics and non diabetics) CKD patients, diabetic CKD patients present inferior survival rates compared with other populations. Becker *et al*[22] have reported that the patient survival benefits of pre-emptive transplantation are more pronounced in LDKT than in DDKT (RR = 0.685; P = 0.001). However renal graft survival did not present significant differences in pre-emptive transplantation except LDKT (RR = 0.81, P = 0,09)[22]. The main reason for these poor outcomes is the accumulated cardiovascular burden during the era before reaching ESRD. Cosio *et al*[35] has shown that diabetic patients who have undergone renal transplantation have significantly increased rates of post-transplant cardiovascular events, cardiovascular mortality and all-cause mortality. It is also noteworthy that most cardiovascular events or deaths usually appear during the first three post-transplant months when the most important complications such as rejection or infections present a peak[8,35,36]. All these data highlight the importance of a thorough pre-transplant evaluation, which may detect early and potentially reversible abnormalities. In addition elderly T2DM patients with advanced CKD may present significantly decreased survival after renal transplantation rising ethical issues regarding allocation policies in an era of graft shortage and increased demand around the world.

Immunosuppressive regimens for T2DM patients do not show any difference compared with other populations. However, there is a current trend for steroid free or steroid avoidance protocols which may not aggravate glycemic control. These policies have not yet been translated into better long-term outcomes.

Hypertension and hyperlipidemia are also highly prevalent in diabetic patients post-transplantation and they should be treated aggressively. However, diabetic transplant recipients present higher rates of hyperkalemia after renin angiotensin system inhibition[4-6].

Glycemic control should also be intensified as hyperglycemia has been associated with worse outcome. However, optimal targets for renal transplantation have not been set yet and transplant physicians usually follow the guidelines for the general population.

SPK TRANSPLANTATION FOR T2DM PATIENTS WITH CKD

By the end of 2010 more than 35000 pancreas transplantations had been reported to the IPTR with the vast majority (24000) performed in the United States[12].

Historically, pancreas transplantation was considered as a relative if not absolute contraindication for T2DM[7]. This concept relied on the pathophysiology of T2DM where insulin resistance has been considered as the prevailing disorder and these patients do not seem to need extra insulin but a better responsiveness of the peripheral tissues to it. However, the classification of diabetes is not always so simple and many patients present with overlapping clinical syndromes. In addition, even in the long-run, not a few T2DM patients may become dependent on exogenous insulin due to pancreatic b-cells exhaustion. Although the classical phenotype of T2DM with CKD is characterized by advanced age and obesity, there are many patients who do not fit on this model and may be seen as candidates for pancreas transplantation.

Initial reports about SPK transplantation in T2DM were based on cases of "unrecognized" T2DM[7]. The IPTR started to be record data about the type of diabetes since 1994. The overall rate of pancreas transplantation in T2DM patients has shown an increase from 2% in 1995 up to 7%

Table 1 Selected data from pancreas transplantation single-center and database studies in type 2 diabetes mellitus patients

Ref.	PTx Era	Number of PTx (*n*)	Age at PTx (yr)	BMI (kg/m^2)	Follow-up (yr)	Pancreas survival rates (yr)	Patient survival rates (yr)
Light *et al*[37]	1989-1999	30 SPK	40 ± 9.3[1] 41.7 ± 6.6[2]	24.8 ± 5.4[1] 25.5 ± 4[2]	3.8	82% (1)[1] 95% (1)[2] 82% (5) 95% (5)	82% (1)[1] 100% (1)[2] 82% (5) 95% (5)
Light *et al*[38]	1989-2004	38 SPK	40 ± 9.3[1] 37.9 ± 8.7[2]	24.8 ± 5.4[1] 23 ± 4.5[2]	> 10	67% (5)[1] 56% (10)[2]	73% (5)[1] 70% (10)[2]
Light *et al*[20]	1989-2008	58 SPK	42.8 ± 8.4	26.1 ± 4.4	> 15-20	58.60% (> 10)	75.8% (> 10)
Nath *et al*[39]	1994-2002	7 SPK 4 PAK 6 PTA	52.5 ± 8.4	27.2 ± 5	4.3	65% (3.3)	94% (1) 71% (3.3)
Singh *et al*[40]	2002-2007	7 SPK	51 ± 2.9	ND	3.3	71% (3.3)	86% (1) 71% (3.3)
Chakkera *et al*[41]	2003-2008	10 SPK	51.9 ± 9	27 ± 3	1.3	100% (1)	100% (1)
Margreiter *et al*[21]	2000-2009	21 SPK	53.6 ± 5.9	25.1 ± 3.3	7.3 ± 3	81.8 (1) 75.9 (5)	90.5 (1) 80.1 (5)
Sampaio *et al*[14]	2000-2007	582 SPK	47 (40-52)	< 18.5 = 2.8% 18.5 to 25 = 43.9% 25 to 30 = 36.2% > 30 = 17.15	3.7	-	67% (5)
Wiseman *et al*[19]	2000-2008	424 SPK	18-34 = 6.1% 35-49 = 54% 50-59 = 39.9%	24.7 ± 2.8	5	87.7 (1) 83.6 (5)	82% (5)

[1]Data for non African-Americans; [2]Data for African-Americans. PTx: Pancreas transplantation; PAK: Pancreas after kidney; PTA: Pancreas transplant alone; SPK: Simultaneous pancreas kidney.

in 2010. According to the same database, in 2010 approximately 8% of SPK, 5% of pancreas after kidney (PAK) and 1% of pancreas transplant alone (PTA) were performed in T2DM patients. T2DM patients who underwent PAK or SPK were older than T1DM patients, whereas there were no age differences between the two groups for PTA. As expected, T2DM patients had a longer duration of DM (22 ± 8 years) and significantly higher BMI[12].

The usefulness of SPK in T2DM patients with CKD can not be justified by evidence from randomized controlled studies and is based on several single center[20,21,37-41] and two recent database studies[14,19] which will be analyzed in details (Table 1). The main problem of all these studies is that they rely on different approaches regarding the classification of diabetes, which are based on several clinical or laboratorial criteria not validated in CKD and different demographics. There is an ongoing debate about the usefulness of C-peptide for the diagnosis of diabetes as there is evidence that not a few T1DM patients may present measurable serum levels[42] and many T2DM patients may also present with undetectable serum levels after many years post-diagnosis. Covic *et al*[43] have confirmed these data in CKD patients making the situation even more complicated.

In addition, traditional exclusion criteria for SPK such as age > 50 years and BMI > 30 kg/m^2 which were applied in the first studies, tend to be ignored in the more recent reports, making the interpretation of the short and long-term outcomes not so easy.

Single-center studies

Light *et al*[37] were the first who attempted to publish pooled data about outcomes of T2DM patients who underwent SPK transplantation. In 2001 they presented data for 30 patients classified as T2DM according to C-peptide levels > 0.8 ng/mL and compared them with a group of 89 patients with lower C-peptide levels over a 10 years period[37]. C-peptide levels were not crucial for the decision to proceed with SPK transplantation in their center. There were no differences between the two groups regarding patient and graft survival rates, although T2DM patients tended to be older and heavier (not statistically significant differences). In 2005 the same group extended their follow-up period and reported outcomes in 38 SPK recipients[38]. Outcomes at 5 and 10 years post transplant did not show significant differences and the authors suggested that decisions about SPK transplants should not be based on C-peptide levels, but on general acceptance criteria. In 2013 they reported a 20 years experience of SPK transplantation based on data from 173 patients[20]. The T2DM group included 58 patients who underwent transplantation from 1989 through 2008 with the same inclusion criteria (C-peptide levels > 0.8 ng/mL). According to this analysis T2DM patients presented better pancreatic graft survival (P = 0.064) but lower patient survival (0.019) during the extended follow-up period. There are no definite explanations for these results, but it is noteworthy that T2DM patients presented lower rejection rates. Moreover, the T2DM group included more African-American and was older, heavier and had a shorter duration of insulin dependence. The authors concluded that C-peptide should not be a marker for SPK candidacy and transplant centers should base their decisions on general criteria which prove whether the diabetic

patient can tolerate the surgical procedure and adhere to the complex follow-up post-transplant.

Nath *et al*[39] reported a cohort of 17 T2DM patients who underwent pancreas transplantation from 1994 through 2002. Seven patients underwent SPK, 4 patients PAK and 6 patients PTA. The authors adopted the american diabetes association and World Health Organization criteria for T1DM and T2DM and did not rely on C-peptide levels[39]. Three patients were on oral hypoglycemic agents at the time of transplantation. Although 1 patient died during the peri-operative period (aspiration pneumonia) the other pancreas recipients presented excellent graft survival rates (94%). Long-term follow up (4.3 years) showed a patient survival rate of 71% and a pancreas survival rate of 63%.

Singh *et al*[40] stratified a cohort of 74 SPK transplants from 2002 through 2007 into two groups according to C-peptide cut-off levels of 2 ng/mL. They wisely did not use the terms T1DM or T2DM but they isolated a subgroup of SPK recipients of "insulin requiring diabetic patients with C-peptide production" for further analysis. So, they reported short- and long-term outcomes in 67 patients with "no" C-peptide (mean 0.2 ± 0.4, range 0-1.9 ng/mL) and 7 patients with C-peptide production (mean 5.7 ± 2.7, range 2.5-9.5 ng/mL). Their selection criteria for SPK transplantation included insulin requirement for at least 5 years, daily dose < 1 U/kg, age < 60 years, and absence of severe comorbid conditions, but not C-peptide levels. Patient survival was better in the "no" C-peptide group at 3 mo, 1 year and last follow-up (40 mo), whereas death-censored kidney and pancreas graft survivals did not present significant differences between the two groups. However, there were significant differences between the two groups before SPK transplantation, which have definitely influenced outcomes. The group with the C-peptide production included more African-Americans, was older, heavier and had a shorter duration of diabetes and a longer dialysis vintage.

Chakkera *et al*[41] reported a cohort study of 80 patients who underwent SPK transplantation from 2003 until 2008. Among them, 10 patients were identified as T2DM patients according to a composite metric which included clinical criteria (absence of ketoacidosis and use of oral antidiabetics), presence of measurable C peptide levels and negative glutamic acid decarboxylase antibodies (anti-GAD65). Patients were eligible for SKP, if BMI was lower than 30 kg/m^2 and needed < 1 U/kg of insulin per day. T2DM patients presented excellent (100%) 1 year pancreas survival as well as T1DM patients (96%) and equal renal graft survival rates after a 16 mo follow-up period. The authors also commented on the usual value of the C-peptide cutoffs in the diagnosis of T1DM (< 0.8 ng/mL) and highlighted that there was a significant overlap of C-peptide levels among T1DM (almost 15% had detectable levels and 8% > 0.8 ng/mL), whereas 30% of the T2DM patients presented low C-peptide levels (< 2 ng/mL) and could be misclassified as T1DM.

Margreiter *et al*[21] have recently reported their experience from 195 T1DM and 21 T2DM patients who underwent SPK transplantation during a nine years period (2000-2009) in Austria. The vast majority (30/32) of the T2DM patients were on exogenous insulin therapy and had a history of oral antidiabetic agents for at least 6 months. Only 2 patients were receiving oral antidiabetics at the time of transplantation. The main criteria for the diagnosis of T2DM were measurable fasting C peptide levels and absence of autoantibodies for diabetes. All patients presented a low cardiovascular risk profile and were eligible for SPK if BMI was lower than 32 kg/m^2. The authors compared outcomes with T1DM patients who underwent SPK transplantation (n = 195) and T2DM patients who underwent DDKT alone (n = 32) during the same period. Although pancreas allograft survival was lower in T2DM patients, it did not reach statistical significance. In a univariate analysis, the T1DM group presented better patient and kidney survival compared with the other groups. However, in a multivariate analysis model the statistical significance was lost, when data were adjusted for various important confounding variables such as donor and recipient age, secondary complications of diabetes, waiting time, delayed graft function etc.

Selected data for comparison from all these studies are shown in Table 1.

Database studies

Sampaio *et al*[14] studied outcomes of SPK transplantation during the period between 2000 and 2007 using data from the UNOS database. Among 6756 SPK transplants there were 582 T2DM cases (8.6%). T2DM patients presented higher rates of delayed kidney graft function and primary kidney non function and inferior rates of 5 year overall (73.5% *vs* 77.8%, P = 0.007) and death censored kidney graft survival 82.9% *vs* 85.3%, P = 0.04) compared with T1DM patients. However, this group included more African-American and Hispanics and the patients were older at diabetes onset and at the time of transplantation, were more often obese and had a higher pre-transplant dialysis time. All these parameters are known to impact transplant outcomes and when data were analyzed after adjustment for confounders, diabetes type could not be identified as a risk factor for all outcomes. In details, hazard ratios were 1.10 (95%CI: 0.86-1.42) for patient death, 1.08 (95%CI: 0.91-1.28) for pancreas allograft failure and 1.16 (95%CI: 0.95-1.39) for kidney allograft failure with T1DM values as reference. Further analysis revealed that increased recipients' age, time spend on dialysis pretransplant and higher BMI were associated with worse outcomes in T2DM patients. However, the study carried a significant limitation regarding the definition of diabetes type which relied mainly on clinical history data and not specified criteria.

Wiseman *et al*[19] analyzed data from 424 SPK transplants in T2DM from 2000 through 2008, using the Scientific Registry of Transplant Recipients database and compared outcomes with patients who underwent LDKT or DDKT. They included in their analysis only recipients aged from 18 to 59 years with a BMI index ranging from 18-30 kg/m^2. Although there were no reliable definitions

of diabetes type in this study, the selection criteria have probably eliminated the percentage of misclassification. In this study the authors reported several very interesting and important results. Although SPK outcomes were excellent even after 5 years post-transplant and looked superior to DDKT, this difference was not due to the pancreas allograft *per se* but to other important factors such as younger allograft kidney donors, younger recipient age and less waiting time for transplantation. In addition the analysis provided a clear 5 year survival advantage in favor of LDKT over SPK. However, the authors acknowledge that the possible advantages of SPK (euglycemia) regarding patient and kidney survival may become clearer after a longer follow-up and patients who undergo SPK may represent a special and probably pre-selected population of T2DM patients. In addition quality of life issues (insulin injections, hypoglycemia, *etc.*) may be more important for several T2DM patients with ESRD than survival. Nevertheless, these data provide clear evidence that LDKT should be considered as a first choice treatment for T2DM patients with CKD and SPK should be seen as a second choice for well selected patients.

Data overview

The results from all these single center and database studies do not provide a clear message about the pros and the cons of SPK in T2DM with CKD and many physicians remain skeptic about its definite role, as it carries significant surgical challenges and it is not an immediately life saving procedure[13,17]. The recently applied UNOS criteria for eligibility of T2DM patients for SPK include only C-peptide levels cut-offs and BMI values (see above), although there is no solid data about this policy[15]. Theoretically, T2DM patients who are eligible for listing for both DDKT and SKT transplantation may be transplanted faster if listed for SPK according to the priority criteria for kidney and pancreas allocation. Nevertheless, it should be emphasized that this theoretical concern may not be proven correct in the real clinical practice, as SPK transplantation is performed only in selected transplant centers and its rates tend to fall over the last years[12].

ISLET TRANSPLANTATION AND T2DM

Islet Transplantation refers to the transplantation of isolated pancreatic islets, which have been harvested from one or more deceased donors. It is not a classic surgical procedure and the islets are infused percutaneously into the portal vein[44].

Allogeneic islet transplantation in humans become popular after the landmark study of the Edmonton group in 2000[44] which showed insulin independence in seven T1DM patients with a steroid free regimen. Nevertheless, these first encouraging results could not be fully reproduced by other centers and patients needed multiple islet transfusions with a long-term success below 10%[45-47]. In addition, the immunosuppressive protocols are potentially nephrotoxic and may be accompanied with a deterioration of the renal function[48,49] whereas the failed islet grafts may lead to recipients' alloimmunization (sensitization) by the production of *de novo* anti-HLA antibodies in titers ranging between 10.8%-31%[48-50]. These poor results have raised skepticism in the transplant community[51] and today only a few centers continue islet transplants on a regular basis in T1DM patients[46,47]. Although the ultimate goal of islet transplantation would be to achieve insulin independence, this remains an exemption and the current goals focus mainly on protection from hypoglycemia, reduction of the daily dose of insulin and correction of HbA1c[47].

Islet transplantation has not been widely applied in T2DM patients. In the literature there is only one report regarding islet transplantation in 5 insulin treated T2DM patients[52]. However these patients were undergoing liver transplantation and islet were given as a possible treatment for coexisting T2DM. Three of them presented normalization of HBA1c and no need for insulin therapy. However, although hypothetical, if clinical data for T1DM patients improve in the future, it would not be a surprise to see islet transplantation applied in T2DM patients, following the example of SPK[17,19].

BARIATRIC SURGERY FOR T2DM PATIENTS WITH CKD

The term "diabesity" has been introduced in the current literature in order to describe the frequent co-existence of T2DM and obesity[53]. Although bariatric surgery procedures tend to increase around the world, there is a debate about its place in the treatment of diabetes[53,54]. Current standards suggest that it has a role in patients with BMI > 35 kg/m^2 with one at least comorbid condition including T2DM[54]. Its theoretical advantages for T2DM patients with lower BMI values remain unproven[53-55]. In addition, there is an ongoing interest regarding the impact of obesity on the pathogenesis and the progression of CKD[56]. However, there is no solid data regarding the beneficial effects of bariatric surgery in CKD, except some small observational single-center studies focusing mainly on the regression of micro- or macro-albuminuria[56,57].

As most transplant centers include obesity (BMI > 30-35 kg/m^2) in the contraindications for renal or SPK transplantation due to excessive surgical complications, many obese T2DM patients may not qualify. So, bariatric surgery has been recently introduced, not as a cure for diabetic nephropathy *per se*, but as a "bridge" for transplantation. There are a few reports about this alternative in patients with advanced CKD, but the complication rates were substantially higher than in non CKD patients[18,58,59]. However these data came from open surgical procedures and currently applied laparoscopic approaches may reduce complications and improve outcomes. Nevertheless, although promising, bariatric surgery in CKD patients or more especially in T2DM patients with CKD has not been studied in depth and should be still considered as experimental[56,60]. If applied, this must be done in specialized and experienced centers under a multidisciplinary

approach.

Nevertheless, a recent analysis of the United States Renal Data System has questioned the current BMI thresholds, as it has shown that even obese diabetic renal transplant recipients may show a survival benefit compared to treatment with dialysis, except patients with BMI > 40 kg/m^2 and obese African Americans[61].

CONCLUSION

Although during the first era of transplant medicine T2DM patients with CKD were considered non eligible for kidney transplantation, recent progress in transplantation medicine has improved their "transplant menu". As pre-emptive kidney transplantation provides a clear survival advantage over dialysis, all patients with no obvious contraindications, should be referred for early evaluation by a transplant center.

There are data that SPK transplantation may be offered in T2DM patients with acceptable long-term outcomes, but it should be noted that the decision is not so easy, as these results come from retrospective studies from very experienced centers and these patients carry particular characteristics (younger ages, no obesity, minimal cardiovascular risk, *etc.*) that may not apply to the average T2DM patient with CKD.

Bariatric surgery may also be considered as a "bridge" to transplantation for very obese T2DM candidates, but at the moment there are no clear data about its outcomes and possible complication rates in this population.

Prospective multi-center studies are warranted in order to clarify all these issues. Until then, the most appropriate transplant option for T2DM patients with diabetic nephropathy should always be individualized, taking under consideration the patient's wills, his overall medical condition and the transplant center's experience with all these procedures.

The transplant menu looks delicious, but we must be a bit more patient.

REFERENCES

1 **Coresh J**, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; **298**: 2038-2047 [PMID: 17986697 DOI: 10.1001/jama.298.17.2038]

2 **Burrows NR**, Li Y, Geiss LS. Incidence of treatment for end-stage renal disease among individuals with diabetes in the U.S. continues to decline. *Diabetes Care* 2010; **33**: 73-77 [PMID: 20040673 DOI: 10.2337/dc09-0343]

3 **Dousdampanis P**, Trigka K, Fourtounas C. Diagnosis and management of chronic kidney disease in the elderly: a field of ongoing debate. *Aging Dis* 2012; **3**: 360-372 [PMID: 23185717]

4 **Luan FL**, Samaniego M. Transplantation in diabetic kidney failure patients: modalities, outcomes, and clinical management. *Semin Dial* 2010; **23**: 198-205 [PMID: 20374550 DOI: 10.1111/j.1525-139X.2010.00708.x]

5 **Guerra G**, Ilahe A, Ciancio G. Diabetes and kidney transplantation: past, present, and future. *Curr Diab Rep* 2012; **12**: 597-603 [PMID: 22872422 DOI: 10.1007/s11892-012-0306-3]

6 **Gaston RS**, Basadonna G, Cosio FG, Davis CL, Kasiske BL, Larsen J, Leichtman AB, Delmonico FL. Transplantation in the diabetic patient with advanced chronic kidney disease: a task force report. *Am J Kidney Dis* 2004; **44**: 529-542 [PMID: 15332226 DOI: 10.1053/j.ajkd.2004.05.030]

7 **Orlando G**, Stratta RJ, Light J. Pancreas transplantation for type 2 diabetes mellitus. *Curr Opin Organ Transplant* 2011; **16**: 110-115 [PMID: 21150617 DOI: 10.1097/MOT.0b013e3283424d1f]

8 **Wolfe RA**, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, Held PJ, Port FK. 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**: 1725-1730 [PMID: 10580071 DOI: 10.1056/NEJM199912023412303]

9 **Boggi U**, Amorese G, Marchetti P. Surgical techniques for pancreas transplantation. *Curr Opin Organ Transplant* 2010; **15**: 102-111 [PMID: 20010103 DOI: 10.1097/MOT.0b013e32833553de]

10 **Boggi U**, Vistoli F, Egidi FM, Marchetti P, De Lio N, Perrone V, Caniglia F, Signori S, Barsotti M, Bernini M, Occhipinti M, Focosi D, Amorese G. Transplantation of the pancreas. *Curr Diab Rep* 2012; **12**: 568-579 [PMID: 22828824 DOI: 10.1007/s11892-012-0293-4]

11 **White SA**, Shaw JA, Sutherland DE. Pancreas transplantation. *Lancet* 2009; **373**: 1808-1817 [PMID: 19465236 DOI: 10.1016/S0140-6736(09)60609-7]

12 **Gruessner AC**. 2011 update on pancreas transplantation: comprehensive trend analysis of 25,000 cases followed up over the course of twenty-four years at the International Pancreas Transplant Registry (IPTR). *Rev Diabet Stud* 2011; **8**: 6-16 [PMID: 21720668 DOI: 10.1900/RDS.2011.8.6]

13 **Sener A**, Cooper M, Bartlett ST. Is there a role for pancreas transplantation in type 2 diabetes mellitus? *Transplantation* 2010; **90**: 121-123 [PMID: 20562677 DOI: 10.1097/TP.0b013e3181e5b7e6]

14 **Sampaio MS**, Kuo HT, Bunnapradist S. Outcomes of simultaneous pancreas-kidney transplantation in type 2 diabetic recipients. *Clin J Am Soc Nephrol* 2011; **6**: 1198-1206 [PMID: 21441123 DOI: 10.2215/CJN.06860810]

15 **Cohen DJ**, Ratner LE. Type 2 diabetes: the best transplant option is still uncertain. *Clin J Am Soc Nephrol* 2012; **7**: 530-532 [PMID: 22442186 DOI: 10.2215/CJN.02120212]

16 **Fourtounas C**, Dousdampanis P. Kidney, Pancreas and Islet Transplant Options for Patients with Diabetic Nephropathy. *J Diabetes Metab* 2013; **S9**: 001 [DOI: 10.4172/2155-6156.S9-001]

17 **Wiseman AC**. Kidney transplant options for the diabetic patient. *Transplant Rev* (Orlando) 2013; **27**: 112-116 [PMID: 23927899 DOI: 10.1016/j.trre.2013.07.002]

18 **Scalea JR**, Cooper M. Surgical strategies for type II diabetes. *Transplant Rev* (Orlando) 2012; **26**: 177-182 [PMID: 22115951 DOI: 10.1016/j.trre.2011.07.002]

19 **Wiseman AC**, Gralla J. Simultaneous pancreas kidney transplant versus other kidney transplant options in patients with type 2 diabetes. *Clin J Am Soc Nephrol* 2012; **7**: 656-664 [PMID: 22344508 DOI: 10.2215/CJN.08310811]

20 **Light J**, Tucker M. Simultaneous pancreas kidney transplants in diabetic patients with end-stage renal disease: the 20-yr experience. *Clin Transplant* 2013; **27**: E256-E263 [PMID: 23480129 DOI: 10.1111/ctr.12100]

21 **Margreiter C**, Resch T, Oberhuber R, Aigner F, Maier H, Sucher R, Schneeberger S, Ulmer H, Bösmüller C, Margreiter R, Pratschke J, Öllinger R. Combined pancreas-kidney transplantation for patients with end-stage nephropathy caused by type-2 diabetes mellitus. *Transplantation* 2013; **95**: 1030-1036 [PMID: 23407544 DOI: 10.1097/TP.0b013e3182861945]

22 **Becker BN**, Rush SH, Dykstra DM, Becker YT, Port FK. Preemptive transplantation for patients with diabetes-related kidney disease. *Arch Intern Med* 2006; **166**: 44-48 [PMID: 16401809 DOI: 10.1001/archinte.166.1.44]

23 **Gruessner RW**, Sutherland DE. Simultaneous kidney and segmental pancreas transplants from living related donors - the first two successful cases. *Transplantation* 1996; **61**: 1265-1268 [PMID: 8610429 DOI: 10.1097/00007890-199604270-00025]

24 **Kasiske BL**, Cangro CB, Hariharan S, Hricik DE, Kerman RH, Roth D, Rush DN, Vazquez MA, Weir MR. The evaluation of renal transplantation candidates: clinical practice guidelines. *Am J Transplant* 2001; **1** Suppl **2**: 3-95 [PMID: 12108435]

25 **EBPG (European Expert Group on Renal Transplantation)**, European Renal Association (ERA-EDTA), European Society for Organ Transplantation (ESOT). European Best Practice Guidelines for Renal Transplantation (part 1). *Nephrol Dial Transplant* 2000; **15** Suppl 7: 1-85 [PMID: 11286185 DOI: 10.1093/ndt/15.suppl_7.2]

26 **Meier-Kriesche HU**, Ojo AO, Port FK, Arndorfer JA, Cibrik DM, Kaplan B. Survival improvement among patients with end-stage renal disease: trends over time for transplant recipients and wait-listed patients. *J Am Soc Nephrol* 2001; **12**: 1293-1296 [PMID: 11373354]

27 **Meier-Kriesche HU**, Arndorfer JA, Kaplan B. The impact of body mass index on renal transplant outcomes: a significant independent risk factor for graft failure and patient death. *Transplantation* 2002; **73**: 70-74 [PMID: 11792981 DOI: 10.1097/00007890-200201150-00013]

28 **Sampaio MS**, Reddy PN, Kuo HT, Poommipanit N, Cho YW, Shah T, Bunnapradist S. Obesity was associated with inferior outcomes in simultaneous pancreas kidney transplant. *Transplantation* 2010; **89**: 1117-1125 [PMID: 20164819 DOI: 10.1097/TP.0b013e3181d2bfb2]

29 **Pham PT**, Danovitch GM, Pham PC. Obesity and its impact on transplantation and alloimmunity. *Transplantation* 2013; **96**: e71-e72 [PMID: 24247903 DOI: 10.1097/01.TP.0000436929.53768.93]

30 **Porubsky M**, Powelson JA, Selzer DJ, Mujtaba MA, Taber T, Carnes KL, Fridell JA. Pancreas transplantation after bariatric surgery. *Clin Transplant* 2012; **26**: E1-E6 [PMID: 22050266 DOI: 10.1111/j.1399-0012.2011.01559.x]

31 **Patel RK**, Mark PB, Johnston N, McGeoch R, Lindsay M, Kingsmore DB, Dargie HJ, Jardine AG. Prognostic value of cardiovascular screening in potential renal transplant recipients: a single-center prospective observational study. *Am J Transplant* 2008; **8**: 1673-1683 [PMID: 18510627 DOI: 10.1111/j.1600-6143.2008.02281.x]

32 **Pavlakis M**, Kher A. Pre-emptive kidney transplantation to improve survival in patients with type 1 diabetes and imminent risk of ESRD. *Semin Nephrol* 2012; **32**: 505-511 [PMID: 23062992 DOI: 10.1016/j.semnephrol.2012.07.014]

33 **Kaufman DB**, Sutherland DE. Simultaneous pancreas-kidney transplants are appropriate in insulin-treated candidates with uremia regardless of diabetes type. *Clin J Am Soc Nephrol* 2011; **6**: 957-959 [PMID: 21527647 DOI: 10.2215/CJN.03180411]

34 **Mange KC**, Joffe MM, Feldman HI. Effect of the use or nonuse of long-term dialysis on the subsequent survival of renal transplants from living donors. *N Engl J Med* 2001; **344**: 726-731 [PMID: 11236776 DOI: 10.1056/NEJM200103083441004]

35 **Cosio FG**, Hickson LJ, Griffin MD, Stegall MD, Kudva Y. Patient survival and cardiovascular risk after kidney transplantation: the challenge of diabetes. *Am J Transplant* 2008; **8**: 593-599 [PMID: 18294155 DOI: 10.1111/j.1600-6143.2007.02101.x]

36 **Lentine KL**, Brennan DC, Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol* 2005; **16**: 496-506 [PMID: 15615820 DOI: 10.1681/ASN.2004070580]

37 **Light JA**, Sasaki TM, Currier CB, Barhyte DY. Successful long-term kidney-pancreas transplants regardless of C-peptide status or race. *Transplantation* 2001; **71**: 152-154 [PMID: 11211183 DOI: 10.1097/00007890-200101150-00025]

38 **Light JA**, Barhyte DY. Simultaneous pancreas-kidney transplants in type I and type II diabetic patients with end-stage renal disease: similar 10-year outcomes. *Transplant Proc* 2005; **37**: 1283-1284 [PMID: 15848696 DOI: 10.1016/j.transproceed.2004.12.215]

39 **Nath DS**, Gruessner AC, Kandaswamy R, Gruessner RW, Sutherland DE, Humar A. Outcomes of pancreas transplants for patients with type 2 diabetes mellitus. *Clin Transplant* 2005; **19**: 792-797 [PMID: 16313327 DOI: 10.1111/j.1399-0012.2005.00423.x]

40 **Singh RP**, Rogers J, Farney AC, Hartmann EL, Reeves-Daniel A, Doares W, Ashcraft E, Adams PL, Stratta RJ. Do pretransplant C-peptide levels influence outcomes in simultaneous kidney-pancreas transplantation? *Transplant Proc* 2008; **40**: 510-512 [PMID: 18374116 DOI: 10.1016/j.transproceed.2008.01.048]

41 **Chakkera HA**, Bodner JK, Heilman RL, Mulligan DC, Moss AA, Mekeel KL, Mazur MJ, Hamawi K, Ray RM, Beck GL, Reddy KS. Outcomes after simultaneous pancreas and kidney transplantation and the discriminative ability of the C-peptide measurement pretransplant among type 1 and type 2 diabetes mellitus. *Transplant Proc* 2010; **42**: 2650-2652 [PMID: 20832562 DOI: 10.1016/j.transproceed.2010.04.065]

42 **Wang L**, Lovejoy NF, Faustman DL. Persistence of prolonged C-peptide production in type 1 diabetes as measured with an ultrasensitive C-peptide assay. *Diabetes Care* 2012; **35**: 465-470 [PMID: 22355018 DOI: 10.2337/dc11-1236]

43 **Covic AM**, Schelling JR, Constantiner M, Iyengar SK, Sedor JR. Serum C-peptide concentrations poorly phenotype type 2 diabetic end-stage renal disease patients. *Kidney Int* 2000; **58**: 1742-1750 [PMID: 11012908 DOI: 10.1046/j.1523-1755.2000.00335.x]

44 **Shapiro AM**, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; **343**: 230-238 [PMID: 10911004 DOI: 10.1056/NEJM200007273430401]

45 **Ludwig B**, Ludwig S, Steffen A, Saeger HD, Bornstein SR. Islet versus pancreas transplantation in type 1 diabetes: competitive or complementary? *Curr Diab Rep* 2010; **10**: 506-511 [PMID: 20830612 DOI: 10.1007/s11892-010-0146-y]

46 **Shapiro AM**. State of the art of clinical islet transplantation and novel protocols of immunosuppression. *Curr Diab Rep* 2011; **11**: 345-354 [PMID: 21830042 DOI: 10.1007/s11892-011-0217-8]

47 **Vardanyan M**, Parkin E, Gruessner C, Rodriguez Rilo HL. Pancreas vs. islet transplantation: a call on the future. *Curr Opin Organ Transplant* 2010; **15**: 124-130 [PMID: 20009930 DOI: 10.1097/MOT.0b013e32833553f8]

48 **Senior PA**, Zeman M, Paty BW, Ryan EA, Shapiro AM. Changes in renal function after clinical islet transplantation: four-year observational study. *Am J Transplant* 2007; **7**: 91-98 [PMID: 17227560 DOI: 10.1111/j.1600-6143.2006.01573.x]

49 **Ferrari-Lacraz S**, Berney T, Morel P, Marangon N, Hadaya K, Demuylder-Mischler S, Pongratz G, Pernin N, Villard J. Low risk of anti-human leukocyte antigen antibody sensitization after combined kidney and islet transplantation. *Transplantation* 2008; **86**: 357-359 [PMID: 18645502 DOI: 10.1097/TP.0b013e31817ba628]

50 **Cantarovich D**, Vistoli F, Bignon JD. Anti-human leukocyte antigen antibodies after islet transplantation: what do they really mean? *Transplantation* 2008; **86**: 204-205 [PMID: 18645479 DOI: 10.1097/TP.0b013e31817ba6e5]

51 **Bromberg JS**, LeRoith D. Diabetes cure--is the glass half full? *N Engl J Med* 2006; **355**: 1372-1374 [PMID: 17005956 DOI: 10.1056/NEJMe068183]

52 **Ricordi C**, Alejandro R, Angelico MC, Fernandez LA, Nery J, Webb M, Bottino R, Selvaggi G, Khan FA, Karatzas T, Olson L, Mintz DH, Tzakis AG. Human islet allografts in patients with type 2 diabetes undergoing liver transplantation. *Trans-*

plantation 1997; **63**: 473-475 [PMID: 9039943 DOI: 10.1097/00007890-199702150-00025]
53 **Dixon JB**, le Roux CW, Rubino F, Zimmet P. Bariatric surgery for type 2 diabetes. *Lancet* 2012; **379**: 2300-2311 [PMID: 22683132 DOI: 10.1016/S0140-6736(12)60401-2]
54 **American Diabetes Association**. Standards of medical care in diabetes--2009. *Diabetes Care* 2009; **32** Suppl 1: S13-S61 [PMID: 19118286 DOI: 10.2337/dc09-S013]
55 **Dixon JB**, Zimmet P, Alberti KG, Rubino F. Bariatric surgery: an IDF statement for obese Type 2 diabetes. *Diabet Med* 2011; **28**: 628-642 [PMID: 21480973 DOI: 10.1111/j.1464-5491.2011.03306.x]
56 **Neff KJ**, Frankel AH, Tam FW, Sadlier DM, Godson C, le Roux CW. The effect of bariatric surgery on renal function and disease: a focus on outcomes and inflammation. *Nephrol Dial Transplant* 2013; **28** Suppl 4: iv73-iv82 [PMID: 24071659 DOI: 10.1093/ndt/gft262]
57 **Heneghan HM**, Cetin D, Navaneethan SD, Orzech N, Brethauer SA, Schauer PR. Effects of bariatric surgery on diabetic nephropathy after 5 years of follow-up. *Surg Obes Relat Dis* 2013; **9**: 7-14 [PMID: 23211651 DOI: 10.1016/j.soard.2012.08.016]
58 **Koshy AN**, Coombes JS, Wilkinson S, Fassett RG. Laparoscopic gastric banding surgery performed in obese dialysis patients prior to kidney transplantation. *Am J Kidney Dis* 2008; **52**: e15-e17 [PMID: 18617303 DOI: 10.1053/j.ajkd.2008.05.016]
59 **Alexander JW**, Goodman HR, Gersin K, Cardi M, Austin J, Goel S, Safdar S, Huang S, Woodle ES. Gastric bypass in morbidly obese patients with chronic renal failure and kidney transplant. *Transplantation* 2004; **78**: 469-474 [PMID: 15316378 DOI: 10.1097/01.TP.0000128858.84976.27]
60 **Modanlou KA**, Muthyala U, Xiao H, Schnitzler MA, Salvalaggio PR, Brennan DC, Abbott KC, Graff RJ, Lentine KL. Bariatric surgery among kidney transplant candidates and recipients: analysis of the United States renal data system and literature review. *Transplantation* 2009; **87**: 1167-1173 [PMID: 19384163 DOI: 10.1097/TP.0b013e31819e3f14]
61 **Gill JS**, Lan J, Dong J, Rose C, Hendren E, Johnston O, Gill J. The survival benefit of kidney transplantation in obese patients. *Am J Transplant* 2013; **13**: 2083-2090 [PMID: 23890325 DOI: 10.1111/ajt.12331]

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