Diploma Thesis

THE IMPACT OF POST-TRANSPLANT DIABETES MELLITUS ON CARDIOVASCULAR OUTCOMES AFTER KIDNEY TRANSPLANTATION

submitted by

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Graz, 30.04.2023

Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, 30.04.2023 *Nora Maria Pinz m.p.*

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Abbreviations

ACE	angiotensin-converting-enzyme
ACS	acute coronary syndrome
ADA	American Diabetes Association
aHUS	atypical hemolytic uremic syndrome
ALG	antilymphocyte globulin
AP-1	activator protein-1
AT1	angiotensin-1
ATG	antithymocyte globulin
BKV	polyomavirus BK
BMI	body mass index
CAI	chronic allograft injury
CD20	lymphocyte antigen CD20
CKD	chronic kidney disease
CKD-MBD	chronic kidney disease- mineral bone disease
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CRP	C-reactive protein
CV	cardiovascular
CVD	cardiovascular disease
CXCL9/10	C-X-C motif chemokine ligand 9/10
Cy-A	cyclosporine-A
DBD	donation after brain death
DCD	donation after cardiac death

DGF	delayed graft function
DM	diabetes mellitus
DNA	deoxyribonucleic acid
DPP4	dipeptidyl peptidase 4
EBV	Epstein-Barr Virus
eGFR	estimated GFR
ERA-EDTA	European Renal Association-European Dialysis and Transplantation Association
ESRD	end stage renal disease
FKBP-12	FK506 binding protein 12
FSGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
GLP1	glucagon-like-peptide 1
HCV	hepatitis C virus
HF	heart failure
IFG	impaired fasting glycemia
IgA	immunoglobulin A
IGT	impaired glucose tolerance
IL-1/2	interleukin 1/2
IL-2-RA	interleukin 2 receptor antagonist
IMPDH	inosine monophosphate dehydrogenase
IQR	interquartile range
IVIg	intravenous immunoglobulin
KT	kidney transplantation
LKD	living kidney donation

MACE	major adverse cardiac event
MEDOCS	medical electronic documentation system
MMF	mycophenolate mofetil
MPA	mycophenolic acid
MPGN	membranoproliferative glomerulonephritis
mTORi	mammalian target of rapamycin inhibitor
NFAT	nuclear factor of activated T-cells
NF-KB	nuclear factor kappa b
NODAT	new onset diabetes after transplantation
NSTEMI	non-ST-elevation myocardial infarction
NTx	Nierentransplantation
OAD	oral antidiabetic drug
ÖBIG	Austrian federal institute of public health/ Österreichisches Bundesinstitut für Gesundheitswesen
ÖDTR	Austrian dialysis and transplantation register/ Österreichisches Dialyse- und Transplantationsregister
ÖGN	Austrian Society of Nephrology/ Österreichische Gesellschaft für Nephrologie
OGTT	oral glucose tolerance test
PCR	polymerase chain reaction
PTDM	post-transplant diabetes mellitus
PTLD	post transplantation lymphoproliferative disorder
RAAS	renin-angiotensin-aldosterone-system
RCT	randomized controlled trial
RR	adjusted relative risk

SGLT2	sodium-glucose-linked transporter 2
STEMI	ST-elevation myocardial infarction
TCG	Transplant Centre Graz
TIA	transient ischemic attack
T2DM	type-2 diabetes mellitus
UAP	unstable angina pectoris

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Zusammenfassung

Hintergrund: Post-Transplantations Diabetes Mellitus (PTDM) ist eine häufige Komplikation nach Nierentransplantation (NTx), welche das kardiovaskuläre und renale Outcome nach NTx negativ beeinflusst. Die österreichische Datenlage bezüglich der Folgen von PTDM und dessen Inzidenz ist limitiert.

Material und Methoden: In dieser retrospektiven Auswertung wurden n=619 PatientInnen, die in unserem Zentrum zwischen 2005-2019 Nierentransplantiert wurden, eingeschlossen. PTDM wurde 52±8 Wochen nach NTx anhand eines pathologischen HbA1c-Wertes (>6,5%), oder einer laufenden antidiabetischen Therapie ohne vorbestehenden Diabetes Mellitus vor NTx, diagnostiziert. Es starben insgesamt 29 PatientInnen innerhalb des ersten Jahres nach NTx, noch vor der Diagnosestellung von PTDM, und wurden deshalb aus der Auswertung ausgeschlossen. Als Outcome-Variable wurde einerseits die kurzfristige Inzidenz von „Major Adverse Cardiac Event (MACE)“, ein kombinierter Endpunkt aus Mortalität, nicht-tödlichem akutem Koronarsyndrom, Herzinsuffizienz oder zerebrovaskulärem Ereignis herangezogen. Anderseits wurde eine Kaplan-Meier Analyse der Langzeitmortalität durchgeführt.

Ergebnisse: Unserer Studienkollektiv - 65,9% männlich - zeigte ein medianes Alter von 51,2 Jahren. Die Prävalenz von Diabetes Mellitus (DM) vor NTx war 14,54%, während die Inzidenz von PTDM 1 Jahr post-NTx 11,63% war. Es benötigten 36,1% der PTDM-PatientInnen eine Insulintherapie, während 65,3% mit oralen Antidiabetika behandelt wurden. Es traten insgesamt 30 MACE-Ereignisse binnen 2 Jahren nach NTx auf. Während einer medianen Nachbeobachtungsdauer von 84 Monaten starben insgesamt 55 Patient*innen, ohne signifikanten Unterschied zwischen den 3 Gruppen (DM, PTDM, non DM), sowohl betreffend MACE (Logrank-test p=0,911), als auch betreffend Gesamtmortalität (Logrank-test p=0,0604). Das durchschnittliche Serumkreatinin lag bei 1,66mg/dl, ohne signifikanten Unterschied zwischen den Gruppen (p=0,2256).

Zusammenfassung: Unsere Studie zeigt in einem großen, österreichischen PatientInnenkollektiv eine PTDM-Inzidenz von 11,2% ein Jahr nach NTx. PTDM hat das kurzfristige kardiovaskuläre Outcome, sowie die langfristige Sterblichkeit, nicht negativ beeinflusst. Die Aussagekraft unserer Ergebnisse ist limitiert durch den retrospektiven Charakter unserer Analyse, sowie der Tatsache, dass der orale Glukosetoleranztest nicht

Teil der routinemäßigen NTx-Nachsorge ist, weshalb die PTDM-Inzidenz unterschätzt werden kann.

Abstract

Background: Post-transplant diabetes mellitus (PTDM) is a common complication after kidney transplantation (KT), which has a negative impact on cardiovascular (CV) and renal outcomes. The Austrian data availability on the consequences of PTDM and the incidence of its occurrence is limited.

Materials and methods: In this retrospective chart-review n=619 patients who received their KT at our centre between 2005-2019 were included. PTDM was diagnosed at 52±8 weeks post-KT through pathological HbA1c-value (>6.5%) or an ongoing therapy with antidiabetic medication at that time without pre-existing diabetes mellitus prior to KT. 29 patients died in the first year post-KT, before PTDM could be diagnosed, thus, they were excluded from the final analysis. The short-term (2-year) incidence of major adverse cardiac events (MACE), a combined endpoint of mortality, non-fatal acute coronary syndrome, heart failure, or cerebrovascular event, was used as an outcome variable. Further, a Kaplan-Meier analysis of long-term mortality was performed.

Results: Our patient collective – 65.9% male – showed a median age of 51.2 years. The prevalence of diabetes mellitus (DM) was 14.54%, while the incidence of PTDM 1-year after KT was 11.63%. 36.1% of PTDM patients used insulin, while 65.3% were treated with oral antidiabetics. MACE occurred in 30 KT recipients within 2 years following KT. During a median follow-up of 84 months, a total of 55 patients died. No significant differences between the three study groups (DM, PTDM, non DM) were found, both concerning MACE (log-rank p= 0.911) and all-cause mortality (log-rank p=0.0604). The mean serum creatinine 1-year post-transplant was 1.66 mg/dl without significant differences between the groups.

Conclusion: Our study shows a PTDM-incidence of 11.63% 1-year post-transplant in a large Austrian patient collective. PTDM had no negative effect on short-term CV outcome or long-term survival. The informative value of our study is limited due to its retrospective character and the fact, that the oral glucose tolerance test (OGTT) is not part of the routine follow-up post-KT, thus, the incidence of PTDM could be underestimated.

1 Introduction

1.1 End stage renal disease

End stage renal disease (ESRD) is defined as an irreversible reduction of a patients renal function that is lethal without dialysis or transplantation. For classification purposes, ESRD is included in chronic kidney disease (CKD) stage 5, which is defined as a glomerular filtration rate (GFR) of less than 15ml/min/1.73m^2 or the requirement of permanent kidney replacement therapy.[1]

Diabetes and Hypertension are the main causes of CKD worldwide.[2] In 2017, the ÖDTR (Austrian Registry of Dialysis and Transplantation), which is run by ÖGN (Austrian Society of Nephrology), published the prevalence of different primary renal diagnoses in patients receiving hemo- or peritoneal dialysis in Austria in their annual report. It shows that about 50 percent of Austrian patients reach dialysis due to diabetic nephropathy or vascular nephropathy caused by chronic hypertension. Other causes of ESRD include hereditary diseases, glomerulonephritis, kidney disease of unknown etiology and interstitial nephritis, as depicted in Figure 1.

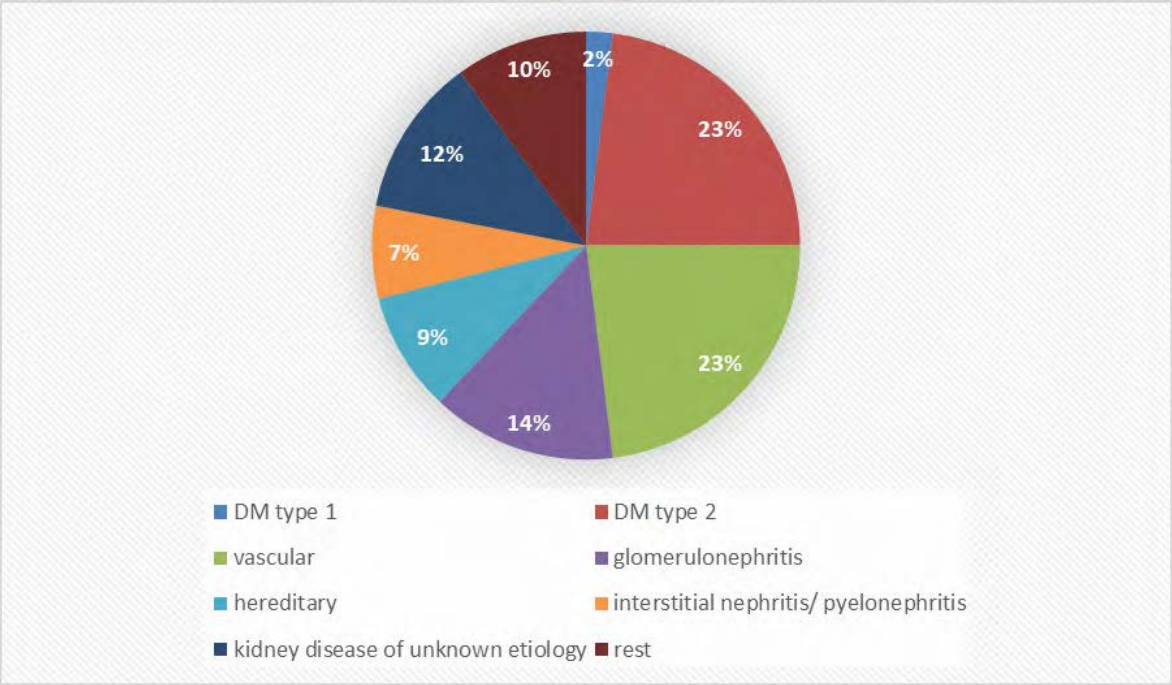

Figure 1: Prevalence of primary renal diagnosis in dialysis patients in Austria in 2017. adopted from ÖDTR 2017[3]

1.1.1 Complications of ESRD

The loss of endocrine and exocrine functions of the kidneys in advanced CKD is associated with the following complications:

Uremia, one of the most common complications of CKD, occurs when a diseased kidney is no longer able to sufficiently excrete substances, which are usually eliminated through the urine (e.g. urea, creatinine, phenols). If dialysis is inadequate, uremic symptoms such as nausea and vomiting, pruritus, anorexia, amnesia, muscle cramps, restless legs syndrome and many more might occur.

The loss of the kidneys ability to regulate the electrolyte-, water- and acid-base balance in advanced CKD leads to metabolic acidosis, fluid retention, and hyperkalemia. The volume overload, in addition to the limited regulation of the blood pressure through the renin-angiotensin-aldosterone system, results in hypertension, which in turn increases rates of cardiovascular (CV) events. The association between GFR and risk of myocardial infarction and CV death was found to be inversely linear. [4]

Normocytic, normochromic anemia regularly occurs in CKD patients, due to diminished erythropoietin synthesis and dialysis related factors, further leading to fatigue and dyspnea.

CKD mineral bone disease (CKD-MBD) is another common complication in advanced CKD. Healthy kidneys regulate the bone and mineral metabolism, both through intestinal absorption of calcium and phosphate, and through excretion via the renal tubular system. CKD-MBD includes abnormalities of serum calcium, phosphate, parathyroid hormone, or the metabolism of vitamin D. This can result in unbalanced bone turnover, or abnormal bone mineralization and growth, which can present itself as bone pain and fragility or calcifications outside the bones (e.g. vascular calcification).[1,4]

1.1.2 Renal replacement therapy

Patients with ESRD require renal replacement therapy, for which 3 options are available: hemodialysis, peritoneal dialysis, and kidney transplantation (KT).[1]

KT is the only cure for ESRD available at present, and therefore the therapy of choice. Transplantation is associated with decreased risk of cardiovascular events, significantly lower overall mortality (figure 2), and improved quality of life, compared to dialysis.

Every patient with CKD stage 4 or 5 with a GFR of less than 20ml/min/1.73m^2 should be evaluated for transplantation.[5,6,7]

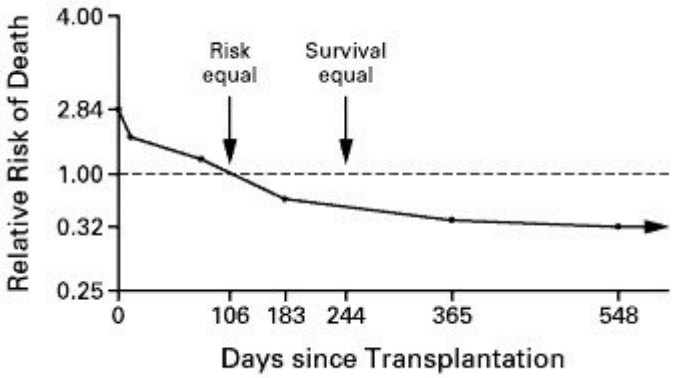

Figure 2: Adjusted relative risk (RR) of death of 23,275 KT recipients of a deceased donor kidney compared to 46,164 dialysis patients on the waitlist (RR 1,0).[8]

Figure 2 shows the adjusted relative risk of death of cadaveric KT recipients. The reference group are patients on the waitlist for transplantation, bridged by dialysis. The points in time where both groups have the same risk of death, and the same probability of survival were marked. The values have been adjusted for gender, age, race, cause of ESRD, year the patient was placed on the waitlist, geographic region, and time between first treatment for ESRD and placement on the waitlist. Straight after transplantation, the risk of death is elevated in the transplantation group, while after one year, their risk of death is 68 percent lower compared to the patients still waiting for transplantation.[9]

1.2 Kidney transplantation

KT is the procedure of surgically removing a kidney from one organism and replanting it into another organism.

There are two different types of kidney donation, the living kidney donation (LKD) and the cadaveric donation, including both donation after brain death (DBD) and after cardiac death (DCD). Living donations occur far less frequent than post-mortem donations. In 2019, 397 kidneys were transplanted in Austria and only 78 of them were LKDs.[10]

1.2.1 Organ donation

In Austria everyone is considered as an organ donor unless they expressed their objection at some point during their life. The objections are registered by the ÖBIG, the Austrian Federal Institute of Public Health. If the patient hasn't clearly stated their will before death, relatives may give information about their presumed volition. The procurement of organs should be performed as soon as possible after brain-death diagnostics in order to minimize ischemic time and avoid organ decay. This leaves the clinicians with no choice but to guide an inconvenient discussion with the donor´s family about organ donation straight after informing them about their loved one´s death, which is a conceivably challenging task. Once the formalities are clarified and consent is given, a transplant coordinator from the nearest transplant centre organizes the explantation procedure and notifies Eurotransplant, the international organ donation agency. The donor or their family can also exclude certain organs from donation due to their belief or for other reasons.[5,11]

1.2.2 Assessment of the donor

The potential donor is extensively examined and evaluated prior to organ procurement to prevent complications for the recipient. Organ quality is assessed through donor age and pre-existing conditions.[5,11] A regional tissue-typing laboratory identifies tissue characteristics and the blood group of the donor.[12]

The functional quality of the organ needs to be quite high because the inevitable damage during the transplantation caused by explantation, cold and warm ischemic time, and implantation, adds to the previously existing damage. The anatomical aspects of the organ, such as the quality and quantity of the arteries and veins supplying the organ, are also inspected. Surgical outcome can largely depend on the quality of the organs vessels, since arteriosclerosis can prevent proper connection with the recipient´s bloodstream, resulting in limited organ function.[5,11]

The organ availability and donor information is reported to Eurotransplant in order to launch the allocation process.

1.2.3 Eurotransplant

The Eurotransplant international foundation runs a database managing the allocation of donated organs in eight European countries. These include Austria, Germany, Belgium,

Hungary, Croatia, Luxembourg, Slovenia and the Netherlands, where this non-profit organization was founded in 1967.[12]

Eurotransplant creates a match-list for each donated organ, based on tissue characteristics, blood group, and medical and organ specific information that is transferred into the central database. A computer algorithm makes sure that each allocation is objective, reproducible, transparent, and valid. The main principles that a match is based on are urgency and expected outcome, while the algorithm also takes the waitlist time and the national organ balance into account, ensuring a fair exchange of organs between the member countries.[12]

1.2.4 Evaluation procedures before admission to the transplant waitlist

In 2007 a consensus meeting was held with representatives from all transplantation centres in Austria to standardize the evaluation of potential kidney transplant recipients. The consensus defined which examinations are necessary prior to being waitlisted for transplantation in a centre in Austria.

Generally, every patient with ESRD without known contraindications should be evaluated for KT. The preliminary examinations should, whenever possible, be started before the patient needs dialysis, ensuring a pre-emptive transplantation. An LKD should be considered in every patient while a combined transplantation can be contemplated whenever diseases of other organs prevent KT.

After a thorough consultation with a doctor, written consent is given by the patient for inclusion on the waiting list for renal transplantation. The consultation must include information on the chances and possible risks of the KT, necessary preliminary examinations, the transplantation itself and necessary treatment after KT.

The evaluation consists of a thorough anamnesis including family history, renal diagnosis and an immunologic assessment considering possible sensitization through blood products, pregnancy, or previous transplants. The anamnesis should uncover contraindications for KT, estimate the patient specific overall risk and potential complications, and determine if additional tests beyond the standard examinations are necessary. Additionally, an estimation of the patients compliance should be performed.

After a clinical status, the patient undergoes several examinations, including both physical and laboratory tests to assess CV, pulmonal, gastrointestinal, urologic, gynecologic, dermatologic, and ophthalmologic health. Additionally, an infectiologic screening

regarding recent and past infections is run, especially considering viral infections that can (re)occur once immunosuppressive medication is administered. The vaccination status of the patient should also be checked.

As a last step, the candidate is subjected to a surgical evaluation. A particular surgical focus is required in case of extensive atherosclerotic vascular status, previous operations, adipositas permagna or in the case of multiple organ transplantation.[13]

1.2.5 Recipient

Once Eurotransplant has made a match, the respective organ is allocated to the transplantation centre responsible for the selected recipient, informing the physicians as well as the transplant coordinator. If the facility decides to accept the offered organ, the recipient is immediately called in for an examination and the subsequent transplantation. Several tests are performed to ensure that the patient does not have any acute infections, newly diagnosed malignancies, or other contraindications for transplantation (see Table 1). Blood is drawn to validate the recipients blood group and for the crossmatch with the donor. [5,11,12]

Absolute Contraindications	Treatable Contraindications
severe untreatable heart disease	active gastrointestinal bleeding
cancer (untreated or systemic)	active acute infections
inoperability	active psychosis
severe degenerative brain disease (e.g. dementia)	
chronic infection (e.g. tuberculosis)	
multisystem disease	
patient non-compliance/ refusal	

Table 1: Contraindications for kidney transplantation. adopted from Kiberd et. al.[14]

1.2.6 Transportation and ischemic time

During the allocation procedure, the donor organs are procured by a surgical team in the respective facility where the donor is hospitalized and are prepared for transportation. The

transportation of the organ is assured in the quickest way possible to keep the ischemic time at a minimum.

Once the kidney is explanted and therefore not perfused anymore, the ischemic time starts, differentiating between warm and cold ischemic time. Kidneys only survive a short amount of time outside the body if stored at body temperature, due to their high oxygen demand. The organ is cooled to the optimal preservation temperature of 0-4° Celsius to lower their energy requirement. Additionally, the kidney is rinsed through with an electrolyte solution to slow cell damage. This allows the kidney to be stored for about 24 hours.

The warm ischemic time is the period in which the organ is not perfused and has body temperature, this mainly consists of the time it takes the surgeon to connect the vessels of the donated organ with the recipients bloodstream. Generally, warm and cold ischemic times should be kept as short as possible, with the warm ischemic time being more significant. [5,11]

1.2.7 Surgical technique

In adults, the surgical incision is made along the lateral side of the musculus rectus abdominis, going in a curve from just above the navel to the midline just above the symphysis pubis.

To expose the common and external iliac artery and vein in the retroperitoneum, the lymphatic vessels are ligated, and the peritoneum is pushed aside. The kidney is transplanted into the iliac fossa and the renal artery and vein are anastomosed to the iliac vessels in an end-to-side fashion, usually starting with the vein.

The placement of the kidney allograft in the iliac fossa and the approximate course of the surgical incision is displayed in Figure 3.

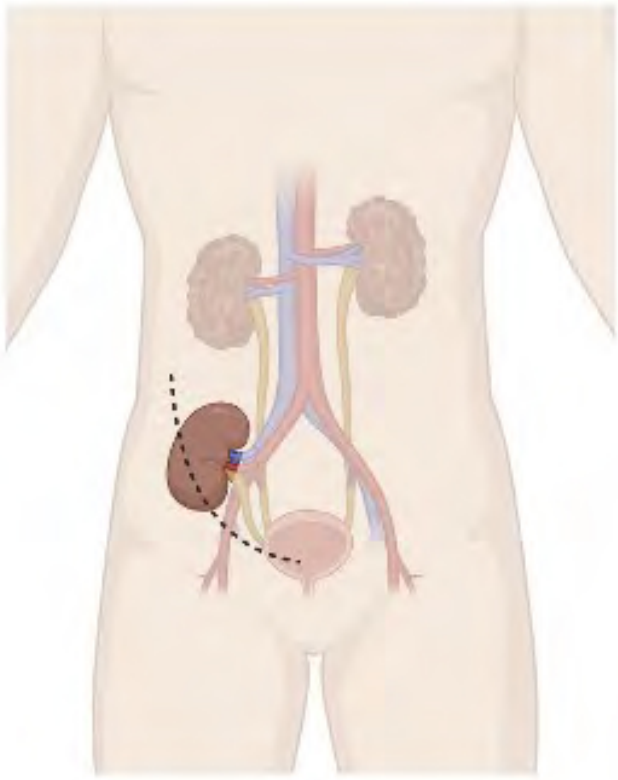

Figure 3: Placement of the kidney in the recipients body. Course of surgical incision. Created with BioRender.com

The clamping of the common iliac vessels, which is necessary for the anastomosis, results in ischemia of the lower extremity and is therefore released as soon as the anastomosis is finished. During this process of reperfusion cold hyperkalemic blood enriched in lactic acid and other products of stasis is released from the extremity into the bloodstream. This can cause temporary hyperkalemia and cardiac malfunction, but these effects are mostly insignificant in adults. The last step of the operation is the anastomosis of ureter and bladder, reconstructing the urinary tract. The patient´s own kidneys are usually not removed.[15]

1.3 Immunosuppression

Immunosuppressive therapy is essential for every kidney transplant recipient to ensure graft survival by inhibiting key steps in the alloimmune response against donor tissue that could otherwise lead to rejection. One can distinguish between induction and maintenance immunosuppression.[16]

Induction immunosuppression can be initiated before, during or straight after transplantation, and serves the purpose of preventing acute rejections. It inhibits or dampens the first T-cell response to antigen presentation of donor tissue. Induction therapy usually consists of an interleukin 2 receptor antagonist (IL2-RA), for example basiliximab or daclizumab, or a lymphocyte depleting agent such as antithymocyte globulin (ATG), antilymphocyte globulin (ALG) or muronomab-CD3.[17]

Compared to maintenance, induction therapy is an intense and powerful highly dosed immunosuppression that is not tolerable for long term use, because of its toxicity. There is sufficient empirical evidence, that patients need highly dosed and potent immunosuppressants early after transplantation, which can be reduced with time.[18]

Maintenance immunosuppression follows induction therapy and is taken lifelong or until graft loss. There are several different agents with different mechanisms of action available. To reduce toxicity of individual drugs while maximizing efficacy, low dosages of several drugs with different mechanisms are combined. Typically, a triple combination including a calcineurin inhibitor (CNI), an antiproliferative agent and a corticosteroid are used as maintenance therapy. Another possible class of immunosuppressants are mTOR inhibitors.[17]

1.3.1 Induction therapy

Induction therapy nowadays usually consists of either basiliximab or ATG. While basiliximab induction has advantages in low immunological risk patients, ATG is preferred in high-risk patients.

Older agents include ALG, which was replaced by ATG, due to its side effect profile. Muromonab-CD3 is a monoclonal antibody against CD3 receptors on T-lymphocytes, that was withdrawn from the market in 2009, while alemtuzumab, a monoclonal antibody against CD52, was withdrawn in 2012.[19]

1.3.1.1 IL-2-RA

Basiliximab is the only clinically available IL-2-RA since daclizumab was withdrawn from the market in 2009.[19,20] Basiliximab is a monoclonal antibody that blocks IL-2 mediated T-cell activation competitively. This is accomplished by binding to the alpha chain of the IL-2 receptor on the surface of activated T-lymphocytes. Thus, a key step of cellular allograft rejection is prevented.[17]

A meta-analysis of 38 randomized controlled trials (RCT) found induction therapy with IL-2-RA to be efficient and safe. In addition to standard immunosuppressive therapy, 17 of these trials compared IL-2-RA with placebo, showing significantly lower rates of acute rejections and improved graft survival while such an effect could not be found for all-cause mortality. Further, IL-2-RA did not increase cytomegalovirus infection rates or malignancies, and had lower adverse effects, compared to other induction therapies. [17,21]

1.3.1.2 lymphocyte depleting agents

ATG are polyclonal antibodies against lymphocytes, obtained from either rabbits or horses. The animals are injected with human thymocytes resulting in antibody production. These antibodies are directed against several surface antigens of T-lymphocytes, resulting in their depletion.[22,23]

ATG shows lower rates of acute rejection in KT recipients with high immunological risk status compared to basiliximab. If compared to no induction therapy or placebo, lymphocyte depleting agents even show fewer graft failures. However, compared to IL-2-RA, they show an increased risk of adverse effects such as infections and malignancies. Thus, lymphocyte depleting agents are usually only preferred in patients with high risk of acute rejection, their beneficial reduction of rejection and graft failure outweighing the risk of serious side effects.[17,24]

Besides increased risk of infection and malignancies, induction therapy with ATG shows adverse effects including cytokine release syndrome, thrombocytopenia, and lymphopenia.[25]

1.3.2 Maintenance therapy

1.3.2.1 Calcineurin inhibitors

CNIs mechanism of action is the inhibition of calcineurin, a key signaling phosphatase of the T-cell proliferation process. They are forming complexes with intracellular proteins, which are then inhibiting calcineurin, stopping it from dephosphorylating the nuclear factor of activated T-cells (NFAT). This prevents gene transcription and T-cell activation, leading to an arrest of the cell cycle between G0 and G1 phase.[20,26,27]

Cyclosporine-A (Cy-A), the first representative of CNIs, is binding cyclophilin, while tacrolimus, the other main agent, is building a complex with FK-binding protein.[26]

Cy-A was first isolated from *Tolypocladium inflatum* in 1969 and represented a revolutionary breakthrough in the field of renal transplantation when introduced in the early 1980ies. Cy-A drastically reduced acute rejections hence improving 1-year and 3-year graft survival.[16,20]

Tacrolimus, a metabolite of the bacterium *Streptomyces tsukubaensis*, was implemented about two decades later in the late 1990ies. It soon proved to be superior to Cy-A in reducing rates of acute rejection 6-12 months after transplantation, which is why it is now predominantly used. [16,20]

Both CNI agents share some adverse effects, one of them is a strong vasoconstricting effect. Through the constriction of the vessels, blood pressure rises and renal perfusion deteriorates, at worst resulting in renal ischemia. Temporary ischemia can cause acute tubular necrosis, if prolonged, it can lead to chronic kidney injury. However, this vascular side effect is dose dependent. CNI induced direct nephrotoxicity, both acute and chronic, remains a huge issue and challenge for long term use, that is still actively researched. [16,20] Other side effects such as hyperlipidemia, hirsutism and hepatotoxicity are occurring more frequently with Cy-A, whilst PTDM, alopecia and neurotoxic effects are more common in tacrolimus. [20,28]

1.3.2.2 Antimetabolites

The working mechanism of this group of drugs is the inhibition of DNA synthesis. It includes mycophenolate mofetil (MMF), mycophenolic acid (MPA) and azathioprine.

MMF is a prodrug that is converted to MPA by gut hydrolysis. MPA is an inhibitor of a key enzyme for de-novo purine synthesis, inosine monophosphate dehydrogenase (IMPDH), hence inhibiting the proliferation of B- and T-cells, which are dependent on de-novo DNA synthesis. Including MMF or MPA into the immunosuppression scheme after KT showed that both substances decrease acute rejections and improve graft outcomes.

Azathioprine, the third antimetabolite, is an analogue of 6-mercaptopurine whose metabolites inhibit de-novo purine synthesis and also have immunomodulating effects.[16,20]

Bone marrow suppression and gastrointestinal side effects often occur with azathioprine administration. Adverse effects of MPA and MMF are quite similar, with the addition of teratogenicity. Thus, azathioprine is used during pregnancy, while MMF/MPA are otherwise preferred, because of their higher efficacy.[20]

1.3.2.3 Corticosteroids

Corticosteroids have been the foundation of immunosuppression since the very first transplantation. The commonly used drug for KT recipients in Austria is aprednislon®. Glucocorticoids have several effects on immune and inflammatory responses, for example decreased secretion of immune response mediators such as interleukine-1 (IL-1), and reduced synthesis of immunoglobin and complement components.[29] The immunosuppressive effect mainly originates from inactivation of the transcription factors nuclear factor kappa b (NF-KB) and activator protein 1 (AP-1), which results in inhibition of the production of proinflammatory cytokines.[30]

Corticosteroids have many well-established adverse effects that open a conversation about avoiding or reducing steroid use. These include the risk of osteoporosis, weight gain, insulin resistance and diabetes, hypertension, hyperlipidemia, atrophy of skin and muscles, cataracts and many more. These effects occur to different extents in various patients, aggravated by high doses, older age, and other pre-existing conditions.[17]

Many studies show that steroid withdrawal leads to an increase in graft loss or graft function loss, with a tendency towards increased acute rejections. Both rapid withdrawal, in the first week after transplantation,[31,32,33] and later withdrawal, after over 3 months,[34,35] have been researched in open-label studies, randomized trials or meta-analyses and have reached similar conclusions.

However, a very recent study (2021) reaches the conclusion, that long term corticosteroid therapy may not be needed in kidney transplant patients with low to moderate immune risk, if a combined, CNI based immunosuppressive therapy is used.[36]

A tendency towards lower rates of metabolic adverse effects, specifically PTDM, was observed in steroid withdrawal or avoidance compared to standard longer steroid use.[33,37]

Overall, steroid withdrawal strategies seem to be more successful since CNIs, antimetabolites and mTOR inhibitors have been implemented, and the type of induction therapy seems to play a role in outcomes.[16]

1.3.2.4 mTOR inhibitors

The mechanism of action of mammalian target of rapamycin (mTOR) inhibitors is the inhibition of the mTOR-signaling pathway that is significant for the cell-cycle of lymphocytes. Rapamycin builds a complex with FK506 binding protein 12 (FKBP-12) that then binds proteins called 'targets of rapamycin', subsequently inhibiting signal transduction at the IL-2 receptor. This prevents the progression of the cell cycle from G1 to S phase.[38]

Sirolimus, also known as rapamycin, is a macrolide derived from *Streptomyces hygroscopicus.* It is one of the clinically available agents for KT while everolimus, a semisythetic derivative of sirolimus, is the second available mTOR inhibitor.[38,39]

The mTOR pathway is not only found in lymphocytes, which explains their broad effects that include anti-inflammatory, antiproliferative, antiviral and antitumoral properties and a variety of side effects.[20]

While mTOR inhibitors themselves are not nephrotoxic, they can aggravate the nephrotoxicity of CNIs in combined therapies. Other adverse effects include stomatitis, wound healing problems, lymphoceles, diarrhea and anemia. However, the main concerns remain their myelosuppressive effect, dyslipidemia and proteinuria.[16,17,20,39]

Many studies are looking for a replacement for CNIs, due to their nephrotoxicity. Since higher acute rejection rates were found in CNI-avoidance strategies, studies nowadays mainly focus on CNI-withdrawal, replacing CNIs a couple of months after transplantation. The CONVERT trial, as well as the ZEUS study, found that conversion from CNIs to mTOR inhibitors resulted in improved graft function with higher GFR after 12 months.

While CNIs were changed to sirolimus in the CONVERT study, and found no differences in graft loss or acute rejection rates, everolimus was used in the ZEUS study, resulting in higher acute rejections. However, looking at long-term outcomes, mTOR inhibitors unfortunately perform worse than CNIs, especially due to significant proteinuria.[40,41,42]

1.3.3 Adverse effects of immunosuppressive therapy

Generally long-term immunosuppression is a balancing act between the many adverse effects and possible graft loss due to rejection. Immunosuppression poses an increased risk of infections, malignancies and cardiovascular disease (CVD). The annual rate of cardiovascular events is up to 50-fold higher in KT recipients compared to the general population and is a common cause of death in recipients with normal transplant function. Immunosuppression needs to be individualized, closely monitored, and adopted, when necessary. However, there are no guidelines for personalizing an immunosuppressive regimen based on personal risk factors, even though long-term outcome greatly depends on it.[17]

An overview of the toxicity profiles of maintenance immunosuppression substances is provided in Table 2.

Adverse effects	Steroids	Cy-A	Tac	mTORi	MMF	Aza
PTDM	+	+	++	+		
dyslipidemia	+	+		++		
hypertension	++	++	+			
proteinuria				++		
decreased GFR		+	+			
diarrhea, nausea, vomiting			+		++	
osteopenia	++	+	(+)			
anemia, leukopenia				+	+	+

Table 2: Overview of adverse effects of maintenance immunosuppression. adopted from KDIGO clinical practice guidelines[17].

Cy-A, Cyclosporine A; mTORi, mammalian target of rapamycin inhibitors; Tac, Tacrolimus; MMF, mycophenolate mofetil; Aza, Azathioprine; PTDM, post-transplant diabetes mellitus; GFR, glomerular filtration rate.

1.4 Complications of KT

1.4.1 Surgical complications

Although the surgical technique of KT has evolved over the past years, surgical complications remain a frequent issue during and after transplantation, increasing both morbidity and mortality of KT recipients.[47] Graft survival is significantly lower in patients with any type of surgical complication.[43]

Nowadays many complications can be prevented by prophylactic correction of abnormalities, that were uncovered either during the evaluation before waitlisting or preoperative assessment. Complications that could not be prevented should be detected early by thorough postoperative monitoring.

One can distinguish between vascular and urologic surgical complications, the latter being more frequent, ranging from 2.5-30 percent.[44,45,46] Urologic surgical complications include urine leakage, ureteral obstruction, and lymphoceles. The incidence of urine leakage after KT differs between transplant centres, possibly due to different types of ureteroneocystostomy used. The complication is resolved through a transcutaneous nephrostomy with the temporary implantation of a Double-J Stent. Ureteral obstruction is usually caused by ischemia of the ureter, and immediate treatment, normally by transcutaneous balloon dilatation and implantation of a temporary stent, is vital for graft survival. Lymphoceles mostly develop due to injury to lymphatic vessels in the iliac region during the operation. The fluid collects between the bladder and the transplanted allograft and is usually reabsorbed spontaneously in asymptomatic patients. In symptomatic patients, the fluid should be drained percutaneously, while a surgical drainage is only necessary in a minority of cases.[47]

Vascular surgical complications are less common than urologic ones, however they often have devastating effects, potentially leading to early graft loss. External iliac artery dissection is a rare complication that can lead to graft loss and ischemia of the lower limb. It can occur intraoperatively or in the postoperative period, and always needs immediate treatment, either surgically or through percutaneous reconstruction. Despite being extremely rare, renal artery thrombosis is responsible for a third of graft losses within one month after KT. Renal artery thrombosis is a complication caused by faulty suture technique in the anastomosis and needs to be explored instantly. Blood flow to the allograft should be restored immediately, otherwise nephrectomy of the graft may be necessary.

Stenosis of the renal artery of the allograft is a frequent complication that leads to hypertension and graft malfunction. Stenosis most times appears months after the KT and can be remedied through balloon dilatation in the majority of cases. Renal vein thrombosis on the other hand occurs in the first few days after KT and often causes graft loss. The first therapy attempt is surgical thrombectomy, however if the restauration of the blood flow is not achieved, a lifesaving nephrectomy is necessary.[47,48]

1.4.2 Delayed graft function

Delayed graft function (DGF) refers to the acute allograft dysfunction occurring in the first week after kidney transplantation, during which dialysis treatment is required.

DGF is a significant complication after KT, and it is associated with poor outcomes, both short- and long-term, leading to higher rates of acute rejection. Additionally, the incidence of DGF is increasing as more expanded criteria donors are used to reduce waitlist time despite organ shortage. While kidneys from deceased donors after brain death show a 30% chance of DGF, the occurrence of DGF in organs from deceased donors after cardiac death is up to 55%.[49]

The most common cause of DGF is acute kidney injury due to ischemic tubular necrosis because of either ischemic injury of the graft before transplantation, or reperfusion issues. Reperfusion can be impaired by surgical vascular complications, either stenosis or leakage of the anastomosis, thrombosis of the renal vessels, hypotension or hypovolemia.[5]

There is evidence that suggests that the innate immune response and following activation of the complement pathway is associated to DGF, further leading to the increase in rejections.

There are several risk factors associated with DGF. They can be divided into donor-related, recipient-related, and perioperative risk factors (see Table 3). Protective factors include living donation, early diuresis, and thymoglobulin induction therapy.[49]

Donor-related	Recipient-related	perioperative
age	dialysis before KT	basiliximab induction therapy
BMI	BMI	combined anesthesia
DCD>DBD	previous KT	
cold ischemic time	ABO incompatibility	
warm ischemic time	panel reactive antibodies	
shipping distance	diabetes mellitus	
African American race	African American race	
expanded criteria donor	male gender	

Table 3: Risk factors for delayed graft function after renal transplantation. adopted from Bahl et al. 2019[49].

BMI, body mass index; DCD, donation after cardiac death; DBD, donation after brain death.

1.4.3 Infections

With the improvement of immunosuppressive regimens after KT, the incidence of acute rejections was drastically reduced, therefore allowing long-term graft and patient survival. However, due to immunosuppression, recipients are more prone to opportunistic infections. In addition, KT recipients are exposed to more pathogens than the average population, as infections obtained from donor tissue or hospital surroundings add to recipient-derived and community acquired infections.[50]

Even though diagnostics and therapy options have evolved over the past years, infections are still dreaded complications after transplantation. In developed countries infections are the second leading cause of death with graft function after cardiovascular disease.[51] A study from Brazil recently showed that infections are even the number one cause of death after renal transplantation in developing countries.[52]

Due to the immunosuppression, signs and symptoms of infection can be very atypical, reduced or even non-existent, making recognition of the disease more difficult. Additionally, infections often progress faster in immunosuppressed patients, and the range

of pathogens potentially responsible is wider, making specific microbiologic germ determination necessary for ensuring the best possible therapy.[50]

The risk of infection is highest in the first six months after KT, especially before the initial highly dosed immunosuppression is tapered. To prevent potential infections during that time, KT recipients receive antimicrobial and antiviral prophylaxis and are regularly screened for infections to make pre-emptive therapy possible.[50] Compared to older age groups, children are more prone to viral infections and have a lower risk of bacterial infection after transplantation, while the general rate of infections is higher in adults.[53] Characteristic infections that emerge despite the standardized prophylaxis in KT recipients and have negative impact on graft function or patient survival are Cytomegalovirus (CMV), polyomavirus BK (BKV) and Epstein-Barr virus (EBV) infections.

CMV is the most common viral infection after KT, and it is associated with a higher risk of long-term graft loss. CMV infection, either primary or reactivated, can have both direct invasive effects and indirect immunologic effects. Invasive effects include CMV syndrome, consisting of fever, myalgia, arthralgia and myelosuppression, and direct inflammation of organs, e.g., nephritis, carditis, hepatitis or colitis, while immunologic effects cause injury or rejection of the allograft, or predispose the organ recipient to other infections. Blood based diagnostics include CMV-serology, however acute infections are usually diagnosed with a PCR test. Ganciclovir is the preferred treatment and either given orally or intravenous.[50,54]

Allograft nephropathy caused by BKV is a common infectious complication, that often leads to chronic graft dysfunction. Patients with a BKV infection rarely show systemic symptoms, which is why a regular PCR screening of BKV replication has been established. The immunosuppression of viremic patients is reduced in order to reduce viral load, however, due to the lack of effective antiviral therapy and the irreversibility of graft fibrosis, chronic graft dysfunction often cannot be prevented.[55]

Another complication associated with a viral infection is PTLD, post-transplantation lymphoproliferative disorder, a group of proliferative disorders of lymphocytes ranging from benign to malignant. A primary infection with the Epstein-Barr virus (EBV) after transplantation puts organ recipients at risk for PTLD, which is reportedly lethal in 40-60 percent of the cases. Fever of unknown origin, mononucleosis-like syndrome, gastrointestinal obstruction and bleeding and infiltration of the graft are possible symptoms

of PTLD. Benign forms of PTLD can be treated by reducing immunosuppressant dosages, while malignant forms need treatment through chemotherapy, radiation, or antibodies against CD20.[50,56]

1.4.4 Renal outcome

Renal outcome after KT is influenced by several factors. The quality of the transplanted organ depends on donor related factors such as age, comorbidities, and anatomical aspects of the kidney (e.g. status of the vessels). Surgical factors including explantation- and implantation techniques, and ischemic times further affect organ quality. Renal outcome also largely depends on recipient-related factors. These include the type of underlying renal condition, and its probability of reoccurrence in the allograft, as well as non-renal comorbidities and the status of their iliac vessels. Acute rejection, chronic allograft injury, or reoccurrence of the underlying kidney disease may limit renal outcomes after KT.

Kidney allograft function can be monitored through regular examination of urine volume, urine protein excretion, serum creatinine, and ultrasound scans of the allograft. An allograft biopsy is recommended, if serum creatinine is persistently elevated without any detectable reason or has not returned to the baseline after treating an acute rejection, or in case of newly occurring proteinuria.

Recipients with specific primary kidney diseases that often reoccur in the allograft should be screened more frequently. These underlying conditions include primary focal segmental glomerulosclerosis (FSGS), IgA nephropathy, atypical hemolytic uremic syndrome (aHUS), and membranoproliferative glomerulonephritis (MPGN).[17]

1.4.4.1 Acute rejection

Acute rejection is an immunologic reaction, either humoral or cellular, of the host against the allograft. Lymphocytes, or antibodies attack and destroy the graft (see Figure 4). If pre-existing antibodies against donor antigens are already in the recipients bloodstream due to previous sensitization, a hyperacute graft rejection, as depicted in Figure 5, is caused.

The main source of screening for acute rejection is serum creatinine, which is an unspecific marker, and therefore needs further clarification, mostly through biopsy of the allograft. Biopsy rules out other sources of graft dysfunction and shows histological changes specific to acute rejection.[17]

However, in recent years non-invasive tools for diagnosis and prediction of acute rejection have been extensively researched in several studies. A systematic review was conducted in 2020, reviewing articles on urinary biomarkers for acute rejection that were published between 2015 and 2020. [57] C-X-C motif chemokine ligand 9 (CXCL9) and 10 (CXCL10) are urinary biomarkers that were assessed in several studies and were found to differentiate patients with acute rejection well, especially if CXCL9 and CXCL10 were used in combination. While the diagnostic accuracy of urinary biomarkers performs well in the setting of clinical studies, they are not yet available in clinical practice.[57]

Acute cellular rejection mediated by T-cells usually responds to corticosteroids, if unresponsive to steroids, or if acute rejection reoccurs, anti-T-cell antibodies can be utilized as treatment.

Acute humoral rejection can be treated with intravenous immunoglobulin (IVIg), anti-CD20 antibodies, anti-T-cell antibodies, or plasma exchange.[17]

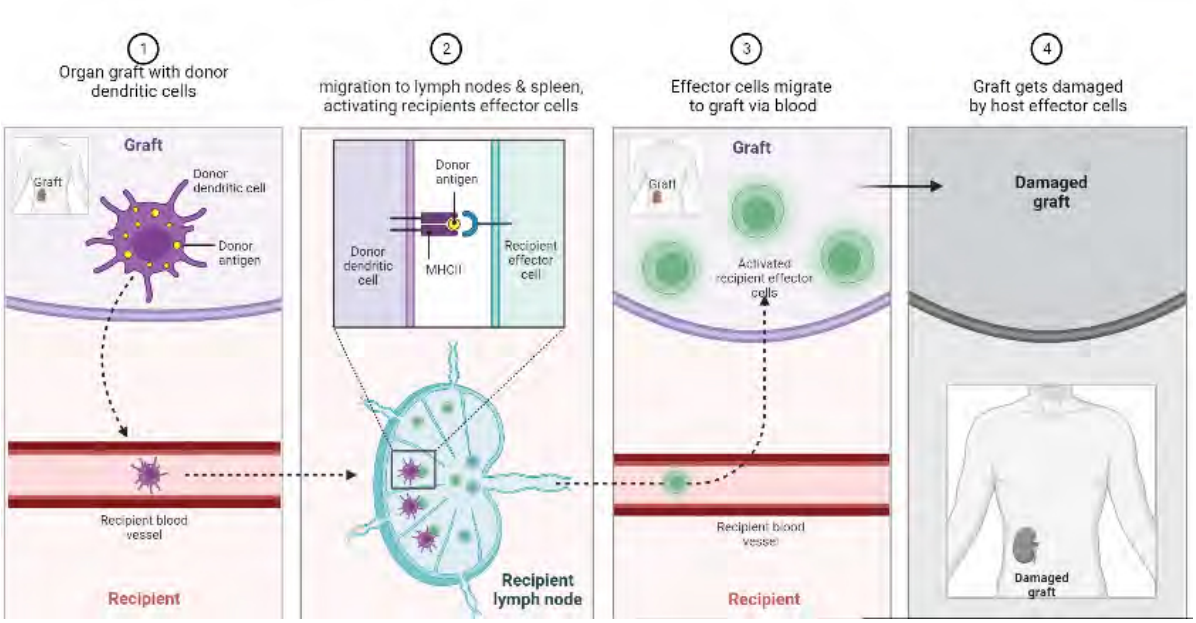

Figure 4: Cellular mechanism of graft rejection. created with BioRender.com

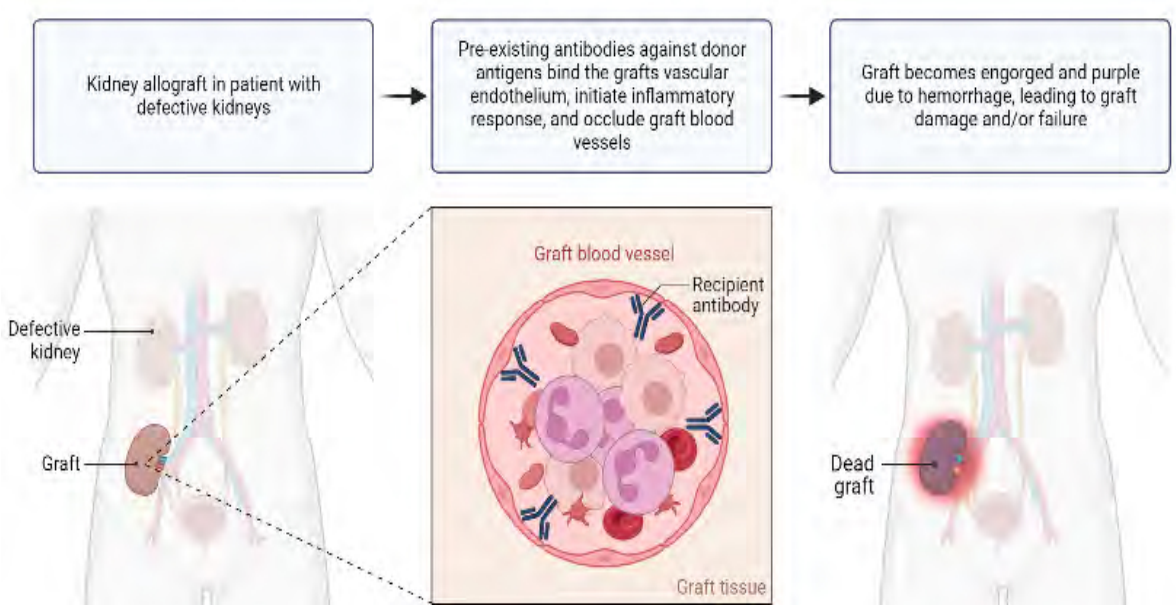

Figure 5: Humoral mechanism of (hyperacute) graft rejection. created with BioRender.com

1.4.4.2 Chronic allograft injury

Chronic allograft injury (CAI) is the main cause of graft loss after KT, followed by acute rejections and reoccurrence of the underlying kidney disease.[17]

CAI includes immunologic and non-immunologic injuries to the allograft, both from the donor or the recipient. Either the tubular epithelium, the endothelium or the glomeruli of the allograft can be affected by the injury. Tissue remodeling and other repair processes are initiated after injury. Chronic inflammation may persist in transplant recipients causing matrix deposition and fibrosis, further leading to malfunction of the allograft and later, failure.[58]

Diagnosis of CAI can be challenging due to its heterogeneous etiology and clinical manifestation. Serum creatinine is used for detection of CAI, but specificity and sensitivity are lacking for early injury. At the time creatinine levels are rising, damage is often already advanced, and reversibility limited. Biopsy of the allograft shows the extent of the damage, but it is often performed too late to prevent chronic injury. Identification of biomarkers that allow detection of early injuries and etiological distinction of CAI is urgently needed to improve outcomes.[58]

1.4.5 PTDM

Post-transplant diabetes mellitus (PTDM) is a common complication after kidney transplantation evoked partially by maintenance immunosuppression. Especially steroids and calcineurin-inhibitors show a connection to the development of this adverse effect. PTDM is one of the most important risk factors for increased all-cause mortality after KT and has a negative impact on cardiovascular and renal outcomes.[59,60]

Due to heterogeneous definitions of PTDM, the incidence of this disease entity is reported to be approximately 10-40%. In 2013 a consensus meeting on PTDM was held in Vienna, where a universal definition of PTDM was agreed upon. This definition has only recently been accepted and implemented by the nephrological and diabetological communities.[61]

PTDM was previously called new onset diabetes after transplantation (NODAT), however, that term excluded the KT recipients that had unrecognized or undiagnosed diabetes prior to transplantation. The term PTDM rectified that by simply referring to the time of diagnosis rather than the time of first occurrence of the disease. [60]

PTDM should only be diagnosed once the allograft function is stable, the KT recipient is steady on their permanent maintenance immunosuppression and has no acute infections. The oral glucose tolerance test (OGTT) is currently considered the gold standard for the formal diagnosis of PTDM. An additional benefit of the OGTT is its potential of detecting impaired glucose tolerance, which independently increases the risk of developing PTDM. HbA1c, the tool that is used to diagnose regular diabetes mellitus (DM), can also be used to detect PTDM. It is a much more practical screening tool, less time consuming and therefore more readily available, compared to an OGTT. However, it is unreliable in the early post-transplantation period due to post-transplant anemia and unstable allograft function and therefore needs confirmation through another diagnostic method in the first year after transplantation. A HbA1c value of 44mmol/mol at 3 months, or 48mmol/mol at 12 months post-transplant is considered adequate for detection of PTDM. 48mmol/mol, or 6.5% respectively, is the same cut-off value that the American Diabetes Association (ADA) uses as a diagnostic criterion for DM in the general population.[59,60]

Many risk factors for developing diabetes mellitus type 2 (T2DM) have also been documented in PTDM patients. As shown in Table 4, these include obesity, genetic predisposition, prior insulin resistance and older age. Predisposing factors that are specific

to the post-transplant period include diabetogenic immunosuppressive medication, infections, and low levels of magnesium. [59,60,61]

General risk factors	Post-transplant specific risk factors
metabolic syndrome (BMI, hypertriglyceridemia, elevated blood sugars, hypertension)	immunosuppression (CNIs, Steroids, mTORi)
central obesity	viral infections (HCV, CMV)
age >40	hypomagnesemia (due to CNIs)
genetic predisposition, family history	
inflammation	
ethnicity (African American, south Asian)	
insulin resistance (impaired glucose uptake in peripheral tissue and suppression of hepatic glucose output)	
pancreatic beta-cell dysfunction (decompensated insulin release)	

Table 4: Risk factors for the development of PTDM. adopted from Jenssen, Hartmann 2019 [59]

BMI, body mass index; CNIs, calcineurin inhibitors; mTORi, mammalian target of rapamycin inhibitors; HCV, hepatitis C virus; CMV, cytomegalovirus.

1.4.6 Cardiovascular disease

CVD is a general expression for conditions concerning the heart, or blood vessels. The major types, which are all present in KT recipients, include coronary heart disease, stroke, congestive heart failure, arrythmias, valvular heart disease and pulmonary hypertension.[62]

CVD is the leading cause of death worldwide in the general population as well as in KT recipients. The cardiovascular risk of an ESRD patient is significantly lowered through KT, compared to waitlisted people with advanced CKD. However, at 3.5-5 %, their annual risk of developing a cardiovascular event is still up to 50-fold higher than in the general population.[61,63]

This elevated risk for cardiovascular complications is due to the sheer number of risk factors KT recipients are exposed to. The prevalence of well-established risk factors such as hypertension, dyslipidemia, obesity, diabetes mellitus and smoking is high in the ESRD

patient population. Interestingly, their prevalence after KT is further increasing, indicating a significant atherogenic and diabetogenic effect of the immunosuppressive agents. Furthermore, disease-specific risk factors of CKD such as low GFR, uremia, homocysteinemia, anemia and proteinuria all contribute to the development of cardiovascular complications through different mechanisms. Uremic toxins in the bloodstream directly injure the endothelium, which initiates the formation of plaques. Additionally, KT-specific risk factors include the atherogenic risk of pre-transplantation dialysis treatment and several post-transplantation metabolic changes. These especially consist of effects of immunosuppressive medication, the development of PTDM, and the impact of allograft dysfunction.[64,65,66]

While cardiovascular screening before waitlisting for KT is standardized in Austria since the consensus meeting in 2007, post-transplantation diagnostics lack standardization. The main focus after transplantation is usually laid on the prevention of acute rejections, optimization of the immunosuppressive regime, and the prevention and treatment of infections, while the proper adjustment of cardiovascular risk factors is often "forgotten". Therefore, CVD remains undertreated despite the known risk it poses.[13,64]

1.5 Objectives of this thesis

PTDM is a common complication after kidney transplantation, and one of the key risk factors for increased mortality in the post-transplant period. PTDM was further shown to have a negative impact on cardiovascular and renal outcomes in previous studies.

Due to heterogeneous definitions of PTDM, there is quite a large variability in the reported incidence of this disease entity, ranging from 10-40 percent.

The aim of this diploma thesis is to perform a retrospective evaluation of KT recipients from our centre with the purpose to obtain a clear picture of PTDM-incidence in our collective. For that, the universal definition of PTDM and the suggestions for diagnostic criteria, that have been agreed upon at the latest consensus meeting in Vienna in 2013, are used.

This thesis further investigates the impact that PTDM has on post-transplantation cardiovascular and renal outcomes in our collective of KT recipients, which will support therapy optimization following KT and, thus, improve future outcomes of KT recipients.

2 Materials and methods

2.1 Study design

We have conducted a retrospective chart-review in our institution. Data was collected in autumn of 2021 from all patients that received their KT at the Transplant Centre Graz (TCG) between the 1.1.2005 and the 31.12.2019.

This study was approved by the ethics committee of the Medical University of Graz (EK Nr 29-111 ex 16/17) and was performed according to the ethical standards of the Declaration of Helsinki. No written informed consent given by the patients was necessary due to the retrospective nature of the study. All collected data was pseudonymized for data evaluation and statistical analysis.

2.2 Patient collective/ Study population

Approximately 50-80 KTs are performed annually at the TCG. We evaluated all ESRD patients that received their KT between 1 January 2005 and 31 December 2019 (n=872) in our centre. As depicted in Figure 6, 619 KT recipients were included in the final analysis. A total of 253 patients were excluded due to reasons as follows: age < 18 years, combined organ transplantation (e.g. pancreas-kidney), loss to follow up after 1 year, or missing/insufficient data available. 29 patients died in the first year post-KT, before PTDM could be diagnosed according to our diagnostic criteria, and were therefore excluded from the analysis.

Altogether, 619 patients were included in the final analysis and were further divided into three cohorts. KT recipients with pre-existing diabetes mellitus (DM), recipients that developed post-transplantation diabetes mellitus (PTDM) and patients without diabetes mellitus (non DM).

In this study we diagnosed PTDM once a stable allograft function was reached at 1-year post-transplantat. We considered either pathological HbA1c values (>48mmol/mol or >6.5%) or the use of diabetes medication (e.g. insulin or oral antidiabetics) without preexisting diabetes mellitus prior to KT. This is in adherence with the latest consensus on PTDM from 2013 in Vienna.[61]

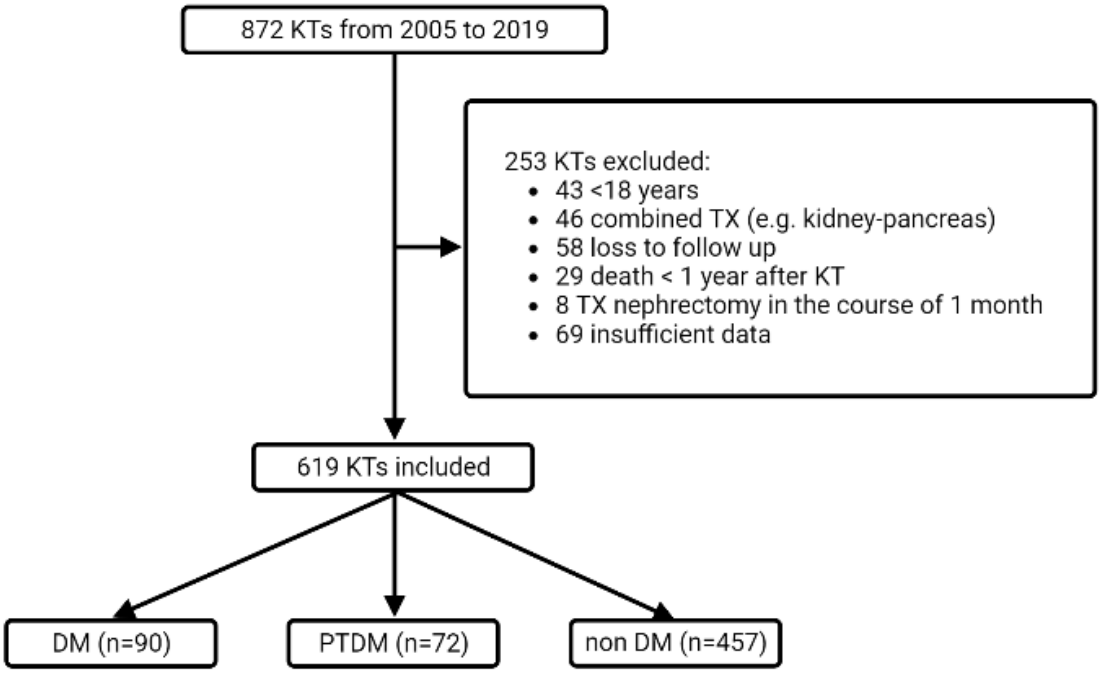

Figure 6: Selection of study participants

KTs, kidney transplant recipients; TX, transplantation; DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus,

2.3 Data collection

The KT recipients from our centre are a well-documented patient population. Basic demographic data and comorbidities of the KT recipients were already available.[67] Patients with type I or type II DM requiring dietary restrictions and/or antidiabetic medication were considered as diabetics.

For this study, medical records were retrieved from the electronic medical documentation system (MEDOCS) of the LKH Graz. Data collected at 1 year after KT included HbA1c-values, diabetes medication (in case necessary), immunosuppressive medication, and medication interfering with the renin-angiotensin-aldosterone-system (RAAS inhibitors) as well as relevant laboratory parameters. All of these values were collected at 52 ±8 weeks after the KT date. Altogether 69 patients were excluded from the study due to missing data (see Figure 6).

For the evaluation of the cardiovascular outcome, the occurrence of a major adverse cardiac event (MACE) in the first two years after KT was defined as a combined endpoint and documented accordingly. Our definition of MACE includes:

- all-cause mortality
- acute coronary syndrome (instable angina pectoris, ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI))
- stroke or transient ischemic attack (TIA)
- hospitalization due to cardiac decompensation

Additionally, a Kaplan-Maier-analysis of long-term mortality was performed.

2.4 Baseline characteristics and comorbidities

Baseline characteristics as well as comorbidities of the KT recipients of our centre have already been collected and analyzed in a previous work.[67]

The data on demographics, primary renal disease, type of dialysis and dialysis vintage – the period between initiation of dialysis and KT, comorbidities and cause of death was obtained from OEDTR, the Austrian Dialysis and Transplantation register. Primary renal disease was categorized with codes of the ERA-EDTA Registry. It was differentiated

between glomerular, tubulointerstitial, diabetic or vascular disease, systematic disease with renal affection, hereditary nephropathy, and miscellaneous underlying disease.

2.5 Statistical analysis

Numerical variables are presented as median and interquartile range (IQR) and are compared using the Kruskal-Wallis test with adequate post-hoc tests. Categorical variables are presented as absolute (n) and relative (%) values within each group and are compared using Chi-squared test. Kaplan-Maier analysis and log-rank tests are performed to assess cumulative MACE and overall mortality probability. The significance level was set to α=0.05. Statistical analysis and figure illustration were performed with Microsoft Excel and the latest version of SPSS.

3 Results

The three study groups (DM, PTDM, non DM) had a median age of 51.2 years at the time of transplantation. The youngest recipient was 18 years old while the oldest one was 83 years old. The study population was predominantly male (65.9%), with only 211 of the included patients being female, while 408 were male. Figure 7 shows the age distribution in our study population.

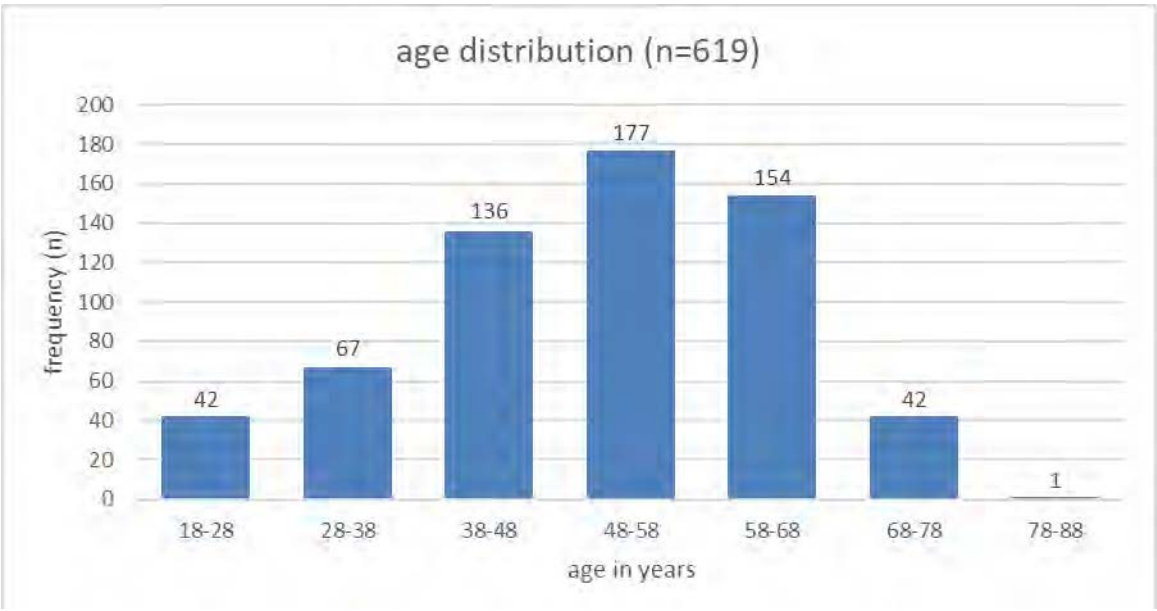

Figure 7: Age distribution in our study population

As shown in Table 5a and Table 5b, the three study groups showed significant differences of certain clinical characteristics, comorbidities, and underlying kidney disease pre transplantation, while other factors were homogenously distributed.

The average age was significantly lower in the non DM group compared to both DM and PTDM ($p<0.001$), and showed the widest range of age with values between 18 and 83 years, containing both the youngest and the oldest study participant. The study population was predominantly male, but showed an even distribution of gender in the different groups ($p=0.6512$). The median BMI was significantly higher in both DM and PTDM patients ($p<0.001$), with an average of 28.66, and 28.08 respectively, compared to non DM patients, whose average BMI was 24.93. Dialysis vintage and the dialysis modality did not differ between the groups, however, the rate of previous KT was significantly lower in the DM and PTDM group (p=0,0001). (see Table 5a)

As shown in Table 5b, the most common primary renal disease in our patient collective was glomerular disease with 31.5%, followed by hereditary nephropathy, vascular kidney disease and miscellaneous kidney disease, all accounting for approximately 15%. The prevalence of diabetic kidney disease was 9.4%.

The frequency of both glomerular disease ($p=0.0046$) and systemic disease affecting the kidneys ($p=0.0124$) was significantly higher in the non DM group, while hereditary nephropathies ($p=0.0003$) and miscellaneous renal disorders ($p=0.0084$) occurred significantly more frequent in PTDM patients. Diabetic kidney disease obviously only occurred in the DM group ($p<0.001$), and renal vascular disease / hypertension and tubulointerstitial disease showed a homogenous distribution between the three study groups.

Baseline Characteristics	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
Age, median (IQR), years	51,20 (18-83)	59,07 (32-73)	55,79 (21-78)	48,93 (18-83)	0,0000
Male sex, n (%)	408 (65,91)	64 (71,11)	51 (70,83)	293 (64,11)	0,6512
BMI, median (IQR), kg/m²	25,84 (16,25-45,31)	28,66 (18,94-45,31)	28,08 (18,08-43,77)	24,93 (16,25-40,61)	0,0000
dialysis vintage, median (IQR), months	57,58 (0-713)	49,69 (0-713)	40,61 (0-305)	61,88 (0-408)	0,3444
Hemodialysis, n (%)	488 (78,84)	77 (85,56)	53 (73,61)	358 (78,34)	0,6773
Peritoneal dialysis, n (%)	92 (14,86)	10 (11,11)	16 (22,22)	66 (14,44)	0,1711
Previous KT, n (%)	120 (19,39)	3 (3,33)	9 (12,50)	108 (23,63)	0,0001

Table 5a: Baseline characteristics and comorbidities

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using the Kruskal–Wallis test for numerical and the Chi-squared test for categorical variables; $P < 0.05$ corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus; IQR, interquartile range; BMI, body mass index.

Underlying renal disease, n (%)	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
Glomerular disease	195 (31,50)	14 (15,56)	18 (25,00)	163 (35,67)	0,0046
Tubulointerstitial disease	49 (7,92)	3 (3,33)	5 (6,94)	41 (8,97)	0,2105
Diabetic kidney disease	58 (9,37)	58 (64,44)	0 (0,00)	0 (0,00)	0,0000
Renal vascular disease/hypertension	89 (14,38)	9 (10,00)	12 (16,67)	68 (14,88)	0,4625
Systemic disease affecting the kidney	37 (5,98)	0 (0,00)	2 (2,78)	35 (7,66)	0,0124
Hereditary nephropathies	95 (15,35)	2 (2,22)	19 (26,39)	74 (16,19)	0,0003
Miscellaneous renal disorders	96 (15,51)	4 (4,44)	16 (22,22)	76 (16,63)	0,0084

Table 5b: Underlying renal disease

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using the Kruskal–Wallis test for numerical and the Chi-squared test for categorical variables; $P < 0.05$ corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus;

3.1 Incidence of PTDM

Out of the 619 KT recipients that were included in the analysis, a total of 72 patients were diagnosed with PTDM according to our definition. Therefore, the PTDM incidence in the

patient collective from our centre is 11.63%. The prevalence of diabetes mellitus prior to KT was 14.54% (n=90), while 73.83% (n=457) of our study population neither had DM before KT, nor developed PTDM.

3.2 Medication 1 year after KT

The usage of certain medication against hypertension at 1-year after transplantation showed no significant differences between the three groups. As shown in Table 6, the use of both ACE inhibitors and AT1 receptor antagonists were similar in the three study groups.

RAAS inhibitor	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
ACE inhibitors, n (%)	163 (26,33)	28 (0,31)	16 (0,22)	119 (0,26)	0,5333
AT1 receptor antagonists, n (%)	85 (13,73)	12 (0,13)	14 (0,19)	59 (0,13)	0,3779

Table 6: Use of RAAS inhibitors at 1-year after KT

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using several Chi-squared tests; $P < 0.05$ corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus; RAAS, renin-angiotensin-aldosterone-system; ACE, angiotensin-converting-enzyme; AT1, Angiotensin 1.

Concerning immunosuppression, the majority (84.65%) of KT recipients received the standard triple immunosuppressive therapy, containing a CNI, a steroid and an antiproliferative agent. The better part (89%) of the 96.6% of patients receiving a CNI used a Tacrolimus based pharmaceutical, mostly Advagraf® or Prograf®, more rarely Envarsus® or Adport®. Only 64 patients (10,7%) received Sandimmun®, which contains Cyclosporine-A.

Table 7 shows, that the PTDM group has a slightly higher proportion of standard triple therapy use, compared to the other groups, however, no significant differences could be detected.

Immunosuppression	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
Standard Triple Therapy, n (%)	524 (84,65)	75 (83,33)	64 (88,89)	385 (84,25)	0,9139
Other regime, n (%)	95 (15,35)	15 (16,67)	8 (11,11)	72 (15,75)	0,6085

Table 7: Prevalence of immunosuppressive regimes

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using several Chi-squared tests; P < 0.05 corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus.

While most recipients (90.95%) received a steroid as part of their immunosuppression, the steroid dosages at 1-year post-transplant varied from as little as 1.25mg up to 50mg per day. As shown in Table 8, the most common doses lay between 5-25mg.

The DM group tended to have lower steroid dosage use (<5mg) more frequently than the other groups (p=0.0526). The average steroid dose was lowest (4.44mg) in the DM, and highest (4.87mg) in the PTDM group, however, the differences were not significant.

Steroid dose	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
< 5 mg, n (%)	164 (26,49)	34 (43,04)	14 (21,21)	116 (27,82)	0,0526
5-25 mg, n (%)	396 (63,97)	44 (55,70)	52 (78,79)	300 (71,94)	0,1245
> 25 mg, n (%)	2 (0,32)	1 (1,27)	0 (0,00)	1 (0,24)	0,3471
Mean steroid dose, mg	4,6875	4,4375	4,8674	4,6957	0,9899

Table 8: Steroid dosages 1-year after KT

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using the Kruskal–Wallis test for numerical and the Chi-squared test for categorical variables; P < 0.05 corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus.

Table 9 depicts the difference in diabetes medication given to regular diabetes mellitus patients compared to PTDM patients. At 1-year post-transplant, 47 of 72 (65.3%) PTDM patients received oral antidiabetics (OAD), while only 26 of 72 (36.1%) of them used insulin. In comparison 75 of 90 (83%) diabetes mellitus patients, the group including both type-1 and type-2 diabetes, received insulin, and 32 of 90 (36%) used OAD.

The most frequently used kind of OAD were dipeptidylpeptidase-4 inhibitors (DPP4 inhibitors) in both groups, while no one received an Alpha-Glucosidase inhibitor or a SGLT2 inhibitor. DM patients used pre-mixed and long-acting insulin significantly more often compared to PTDM patients (p= 0.0015 and p= 0.0092 respectively).

Diabetes medication	Total (n=619)	DM (n=90)	PTDM (n=72)	p-Value
Insulin, n (%)	101 (16,32)	75 (83,33)	26 (36,11)	0,0002
long-acting	61 (9,85)	44 (48,88)	17 (23,61)	0,0092
short-acting	59 (9,53)	41 (45,55)	18 (25,00)	0,0312
pre-mixed	31 (5,01)	26 (28,88)	5 (6,94)	0,0015
OAD, n (%)	79 (12,76)	32 (35,55)	47 (65,27)	0,0071
Metformin	5 (0,81)	3 (3,33)	2 (2,77)	0,1516
Sulfonylurea	8 (1,29)	3 (3,33)	5 (6,94)	0,0500
Glinides	1 (0,16)	0 (0,00)	1 (1,38)	0,3173
Alpha-Glucosidase inhibitors	0 (0,00)	0 (0,00)	0 (0,00)	
Glitazone	1 (0,16)	0 (0,00)	1 (1,38)	0,3173
SGLT2 inhibitors	0 (0,00)	0 (0,00)	0 (0,00)	
GLP1 Receptor Agonist	1 (0,16)	1 (1,11)	0 (0,00)	0,3898
DPP4 inhibitors	67 (10,82)	28 (31,11)	39 (54,16)	0,0234

Table 9: Diabetes medication at 1-year after KT

Comparisons of variables between the study groups (DM, PTDM) were performed using several Chi-squared tests; $P < 0.05$ corresponds to statistically significant differences between the two groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; OAD, oral antidiabetic drug; SGLT2, sodium-glucose-linked transporter 2; GLP1, Glucagon-like-peptide; DPP4, dipeptidyl peptidase 4.

3.3 Cardiovascular outcome

The post-transplant combined endpoint (MACE) was reached in 5 of 90 DM patients (5.56%), 4 of 72 PTDM patients (5.56%), and 21 of 457 non DM patients (4.6%). In total, 30 major adverse cardiac events occurred within 2 years after KT, which represents a 2-year cumulative MACE incidence of 4.85% in our study collective. Notably, n=29 patients died within the first year after KT prior to PTDM diagnosis and were therefore excluded from the endpoint- und survival analysis. No significant differences could be observed between the three study groups concerning the incidence of MACE (p=0.8924).

As Table 10 depicts, the number of individual events, that together form MACE, did not significantly differ between the DM, PTDM and non DM groups. (p=0.2724 for all-cause mortality, p=0.8065 for acute coronary syndrome (ACS), p= 0.5504 for Stroke/TIA, p=0.1666 for heart failure (HF)).

Altogether, the study population showed a low mortality rate without significant differences between the three study groups.

Outcomes	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
MACE, n (%)	30 (4,85)	5 (5,56)	4 (5,56)	21 (4,60)	0,8924
All-cause mortality, n (%)	11 (1,78)	3 (3,33)	0 (0,00)	9 (1,97)	0,2724
Infection	4 (0,65)	1 (1,11)	0 (0,00)	3 (0,66)	0,6815
CV	4 (0,65)	0 (0,00)	0 (0,00)	4 (0,88)	0,4922
Malignancy	0 (0,00)	0 (0,00)	0 (0,00)	0 (0,00)	
Other	3 (0,48)	1 (1,11)	0 (0,00)	2 (0,44)	0,5774
ACS, n (%)	9 (1,45)	2 (2,22)	1 (1,39)	6 (1,31)	0,8065
Unstable AP	3 (0,48)	1 (1,11)	0 (0,00)	2 (0,44)	0,5774
NSTEMI	4 (0,65)	0 (0,00)	1 (1,39)	3 (0,66)	0,5497
STEMI	2 (0,32)	1 (1,11)	0 (0,00)	1 (0,22)	0,3471
Stroke/TIA, n (%)	7 (1,13)	0 (0,00)	1 (1,39)	6 (1,31)	0,5504
HF, n (%)	7 (1,13)	2 (2,22)	2 (2,78)	3 (0,66)	0,1666

Table 10: Rate of MACE within 2 years after KT

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using several Chi-squared tests; $P < 0.05$ corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus; MACE, major adverse cardiac event; CV, cardiovascular; ACS, acute coronary syndrome; unstable AP, unstable angina pectoris; NSTEMI, Non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; HF, heart failure.

During a median follow-up of 84 months, a total of 55 patients died, 3 of 72 (4.2%) in the PTDM, 13 of 90 (14.4%) in the DM and 39 of 457 (8.5 %) in the non DM group.

The Kaplan-Meier analysis showed no significant difference between the three study groups, both in terms of MACE occurrence (log-rank test p=0.911) and in terms of long-term all-cause mortality (log-rank test p= 0.0604). (see Figure 8 and Figure 9)

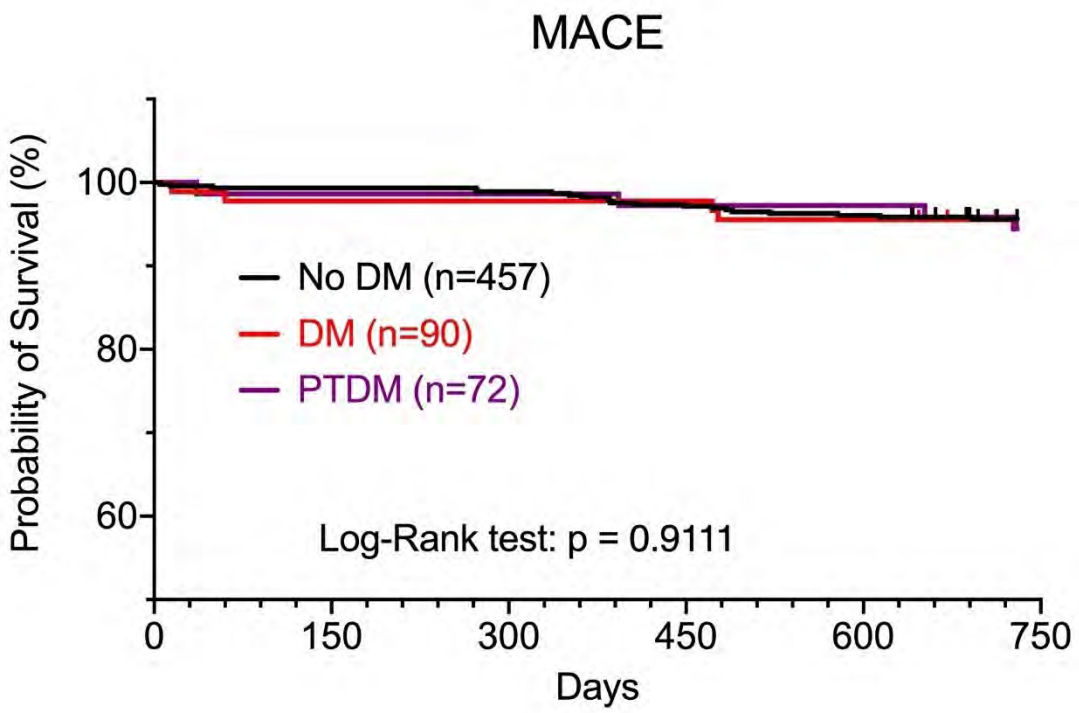

Figure 8: Kaplan-Meier analysis of the 2-year MACE incidence post-KT

MACE, major adverse cardiac event; DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus.

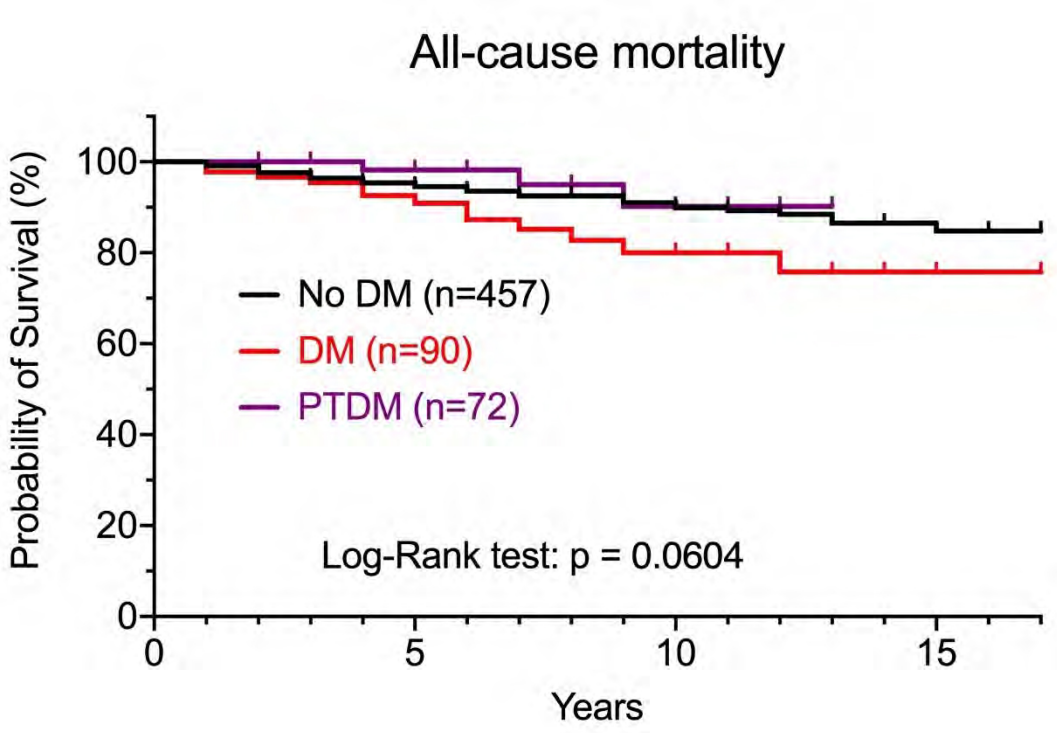

Figure 9: Kaplan-Meier analysis of the long-term all-cause mortality.

DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus.

3.4 Renal outcome

The mean creatinine in our study population at 1-year post-transplant was 1.66mg/dl, without significant differences between the three study groups (p=0.2256). (DM 1.60mg/dl; PTDM 1.74mg/dl; non DM 1.67mg/dl).

In contrast, the mean HbA1c value, as expected, showed significant differences between the three groups (p<0.0000). The HbA1c mean was highest in the DM group with 56.71mmol/mol, followed by the PTDM group with 48.53mmol/mol, and 36.39mmol/mol in the non DM group. (see Table 11**)**

	Total (n=619)	DM (n=90)	PTDM (n=72)	non DM (n=457)	p-Value
HbA1c, median (IQR), mmol/mol	40,76 (22-97)	56,71 (34-92)	48,53 (30-97)	36,39 (22-47)	0,0000
Creatinine, median (IQR), mg/dl	1,66 (0,6-14,3)	1,60 (0,69-6,64)	1,74 (0,83-7,8)	1,67 (0,6-14,3)	0,2256

Table 11: Mean creatinine and HbA1c values

Comparisons of variables between the study groups (DM, PTDM, non DM) were performed using several Kruskal–Wallis tests; P < 0.05 corresponds to statistically significant differences between all three groups. DM, diabetes mellitus; PTDM, post-transplant diabetes mellitus; non DM, no diabetes mellitus; IQR, interquartile range; HbA1c, hemoglobin A1c.

4 Discussion

The primary goal of this monocentric retrospective study was to identify the incidence of PTDM in our collective of KT recipients, using the new PTDM-definition according to the latest consensus. Using the HbA1c value and/or the use of OAD without pre-existing DM for diagnosis, the incidence in this big Austrian collective was 11.56%. However, the OGTT is not part of the standard routine KT follow up in our centre in Graz, therefore the incidence could be underestimated. Additionally, we had to exclude some KT recipients from our study, since the HbA1c value was not measured within the defined time-period of 52 ±8 weeks after KT.

Paek et al. observed a very similar incidence of PTDM at 11.8% in a nationwide Korean cohort study including 723 KT patients in 2019. They used the exact same diagnostic criteria for PTDM that we did.[68] In comparison, Malik et al. found a cumulative PTDM incidence of 29% 5-years after KT and no association between PTDM and graft-failure or death in their multicentric chart-review based study including 632 adult KT recipients in 2021. Their diagnostic criteria included the documentation of PTDM in medical records besides HbA1c value >6.5% or antidiabetic medication without pre-existing DM. It seems improbable that this small difference of diagnostic criteria explains such a big variance. However, they diagnosed PTDM biannually for 5 years, starting at 6 months post-transplantation, therefore allowing the PTDM incidence to vary over time. At 1-year post-transplant the incidence was only 18.5%. [69] It is not recommended to diagnose PTDM only based on HbA1c value before 1-year after KT, as transient hyperglycemia after KT could possibly be misdiagnosed as PTDM, which could explain the higher incidence of PTDM found by Malik et al. [61]

Another goal of the current study was to investigate the association of PTDM with cardiovascular mortality. The short-term incidence of MACE, a combined endpoint of mortality, non-fatal acute coronary syndrome, heart failure, or cerebrovascular event, was used as the cardiovascular outcome variable. The total MACE incidence within a 2-year follow up was 4.85% in our collective. This is several percent lower compared to the MACE incidence found in the same population of KT recipients in a previous study from Deak et. al. conducted at the Medical University of Graz. In that study, which investigated the impact of cardiovascular risk stratification strategies in KT over time, the 2-year cumulative MACE incidence was 8.7%, even though it followed the same definition as this

study. [67] This can be explained by the exclusion of n=29 KT recipients, who died within the first year following KT and, thus, were undiagnosed of PTDM.

Due to low MACE incidence, we were unable to find a clear link between PTDM and cardiovascular mortality in our study population. This is in contrast to several studies which already proved that the development of PTDM or impaired glucose tolerance (IGT) worsen graft function post-transplantation and, thus, enhance CV morbidity and mortality. [70,71,72]

Porrini et al. found prediabetes present at 12 months post-transplantation to be an independent risk factor for cardiovascular events. In their study, the risk of prediabetes patients was twice as high compared to patients with normal glucose metabolism. The observed risk of cardiovascular disease and the survival curves were similar in the prediabetes and PTDM groups. [73]

Valderhaug et al. observed an association between IGT 10 weeks after KT and risk for total mortality but not with cardiovascular disease, in their study of 1410 KT recipients who underwent OGTTs repeatedly.[71] However, Wauters et al. observed a significant correlation independent of other risk factors between impaired fasting glycemia (IFG) 12 months after KT and risk of MACE and strokes. Moreover, the risk of death due to MACE was found to be greater in patients with hyperglycemia. [72]

The randomized controlled DAPA-CKD trial recently achieved a major breakthrough in the field of nephrology, when they found dapagliflozin, a SGLT-2 inhibitor, to be very effective in the improvement of renal outcome both in diabetic and non-diabetic CKD patients. Dapagliflozin inhibits Sodium glucose transporters in the proximal tubules and therefore increases renal glucose elimination in hyperglycemic patients. The study found a significant difference in outcome between the CKD patients who received dapagliflozin compared to the placebo group, regardless of their diabetes status. Those who received dapagliflozin had a reduced risk of developing ESRD, experiencing a significant decline in the eGFR (> 50%) or dying from renal or CV causes. [74] However, while dapagliflozin is now approved for the treatment of diabetic and non-diabetic CKD, little is known about whether this agent can safely and effectively be used in KT patients. The major RCTs all excluded KT recipients due to safety concerns, and thus, the question whether the beneficial effects outweigh the potential risks remains unanswered. [75]

5 Limitations and strengths

Our study was a retrospective, chart-based analysis, thus, the usual limitations of this study design are present. The exclusion of patients due to missing data may potentially cause selection bias. Furthermore, only associations can be described in retrospective studies. To verify the causality of our findings, prospective studies are necessary in the future.

Another limitation is the relatively low incidence of PTDM compared to other studies, resulting in an inhomogeneous group distribution. The low incidence of PTDM cases is explained due to the cross-sectional screening strategy based on pathological HbA1c values, as these data were available to detect. This also highlights the importance of regular oGTT screenings following KT, which should be integrated in the clinical routine of our outpatient clinic. Additionally, the total number of MACE events was small in our study collective, due to the exclusion of 29 patients who died before the PTDM diagnosis.

Although we designed a monocentric evaluation, we managed to include a reasonably large number of KT recipients over a long observational period between 2005 and 2019. Additionally, the data collection was done thoroughly over the years with different main focus, therefore illuminating many aspects after KT. A wide spectrum of transplant specific parameters was collected, allowing different perspectives on KT outcomes. The strengths of this study further include the decently long follow-up period for long term mortality (84 months).

6 Conclusion

Ultimately, this retrospective study revealed a post-transplant diabetes mellitus incidence of 11.63% in our transplant centre in Graz. We could not show any significant associations between MACE occurrence and diabetes status, neither pre-existing diabetes mellitus nor post-transplant diabetes mellitus, in our study population. However, the three groups showed significant differences in certain clinical characteristics, comorbidities and their underlying kidney diseases. First, the DM and PTDM patients were distinctly older (59.07 and 55.79 years compared to 48.93 years), and their BMI was significantly higher with a mean of 28.66, and 28.08 respectively, compared to 24.93 in non DM patients. Further, KT recipients with glomerular disease or a systemic disease affecting the kidneys as their underling renal disease were found to develop PTDM less frequently, while patients with hereditary nephropathies or miscellaneous kidney diseases seemed to be more prone to develop PTDM.

Regarding future research, it would be of interest to examine the causality of our findings with a prospective approach, and to expand the study collective with a multicentric study design. Furthermore, regular oGTT screenings should be integrated into the routine KT follow-up in our outpatient clinic, as the incidence of PTDM could be determined more precisely using this diagnostic criterion. To better reveal the association between CV mortality and PTDM, the observational period for MACE events should be prolonged in future studies to ensure a higher MACE incidence.

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