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## Actual aspects of pancreas and kidney transplantation



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Michael Mikhailov  
aus Minsk

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Berichterstatter: Prof. Dr. med. Axel Kleespies

Mitberichterstatter: Prof Dr. med. Antje Habicht  
PD Dr. med. Jan-Michael Abicht

Dekan: Prof. Dr. med. Thomas Gudermann

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Berlin, den 27.05.2022

Michael Mikhailov

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## List of abbreviations

TBI	total body irradiation
EC	enteric conversion
SPK	simultaneous pancreas-kidney transplantation
ED	enteric drainage
BD	bladder drainage
LDKT	living donor kidney transplantation
TPG	German Transplant Act

## List of dissertation-relevant publications

Kleespies A, Mikhailov M, Khalil PN, Preissler G, Rentsch M, Arbogast H, Illner WD, Bruns CJ, Jauch KW, Angele MK. Enteric conversion after pancreatic transplantation: resolution of symptoms and long-term results. *Clin Transplant* 2011;25:549-560.

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\*Equal contributors

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\*Equal contributors

## 1. Zusammenfassung

Die Transplantation gehört zu komplexesten und anspruchsvollsten Bereichen der Medizin. Nur durch die Organtransplantation kann ein nichtfunktionierendes Organ auf weitgehend physiologischer Weise ersetzt werden. Der Erfolg einer Organtransplantation hängt jedoch von sehr vielen unterschiedlichen Aspekten ab. Nicht nur chirurgische Aspekte (Technik der Organentnahme und Transplantation, Anastomosentechniken, Beherrschung von Komplikationen), sondern auch immunologische Aspekte (Immunsuppression und Therapie einer Abstoßung), und eine ganze Reihe psychologischer Faktoren spielen hier eine zentrale Rolle. Die in der Dissertation präsentierten Studien untersuchen Einige dieser Aspekte der Organtransplantation.

Die erste Studie untersucht die Inzidenz, perioperative Morbidität und Langzeitergebnisse einer chirurgischen Notfallprozedur, der sogenannten „cysto-enterischen Konversion“ an 32 Patienten nach Pankreas-Nierentransplantation. Die cysto-enterische Konversion wird durchgeführt, wenn eine Pankreastransplantation mit früher regelhaft durchgeführter „Blasendrainage“ (Ableitung des Pankreassaftes in die Harnblase) zu massiven Symptomen führt. Die vorliegende retrospektive Studie untersucht die bis dato größte Patientenkohorte mit cysto-enterischer Konversion außerhalb der USA. Die cysto-enterische Konversion führte in unserer Kohorte (Klinikum Grosshadern) auch viele Jahre nach primärer Pankreastransplantation zu einer kompletten oder signifikanten Symptomlinderung bei weiterhin guter Transplantatfunktion, hoher Zufriedenheit der Patienten und gutem Patientenüberleben.

In der zweiten Studie untersuchten wir einen möglichen Einfluss von Mondphasen und Tierkreiszeichen auf die Kurz- und Langzeitergebnisse nach einer Lebendspende-Nierentransplantation. Nicht wenige Patienten wünschen im Rahmen der geplanten Organspende und -transplantation eine individuell abgestimmte OP-Planung. Auch die Berücksichtigung von Mondphasen spielt hierbei eine zunehmende Rolle. So glauben 17.5% der Süddeutschen Bevölkerung, dass Mondphasen die Ergebnisse einer Operation beeinflussen können. Die vorliegende umfassende Analyse von 278 konsekutiven Lebendspende-Nierentransplantationen am Klinikum Grosshadern kann jedoch keinen Zusammenhang zwischen Mondphasen, Tierkreiszeichen und perioperativen Komplikationen, Organfunktion, Patientenüberleben und Langzeitergebnissen nachweisen.

Diese Ergebnisse können zur Aufklärung und Beruhigung von Spender und Empfänger verwendet werden.



## 2. Summary

Organ transplantation is the most physiological approach to replacement of dysfunctional organs. It is also one of the most challenging and complicated areas of medicine. Successful transplantation depends on numerous aspects: surgical (successful transplantation surgery and management of possible complications), immunological (management of immune response), psychological and many others. Some of these aspects are investigated in the studies presented in the current thesis.

The first study was designed to analyze the incidence, indications, complications and long-term results of enteric conversion in 32 recipients of simultaneous pancreas-kidney transplants at a single institution. Enteric conversion is a surgical procedure, that is applied for the treatment of symptoms associated with the bladder drainage technique, that was used earlier for the management of exocrine secretions of pancreatic grafts. The retrospective study (the biggest experience with enteric conversion outside the US) showed, that enteric conversion, performed even years after primary pancreas transplantation resulted in excellent long-term function of pancreatic grafts and complete or at least significant resolution of preoperative symptoms.

The aim of the second study was to investigate a possible influence of particular moon cycle parameters on short- and long-term outcome of living donor kidney transplantation, since a considerable number of patients wish to optimize the timing of the procedure according to the moon calendar. The results of this retrospective analysis of 278 consecutive transplantation procedures performed at a single institution demonstrated no such influence and can be used by surgeons to relieve patients' concerns about the wrong timing of surgery, since the superstition that the moon cycle might impact surgery outcome is quite popular in the southern part of Germany, with 17.5% of patients believing in it.

### 3. Introduction

Transplantation is currently one of the best therapies for the replacement of dysfunctional organs. Its idea had been around for hundreds and even thousands of years, starting with the legend of the leg transplantation performed by Cosmas and Damian (Piza-Katzer et al. 2009). However, the systematic research in transplantation medicine has started relatively recently, in the beginning of the 20<sup>th</sup> century.

The first steps of transplantation research were done in the field of transplantation surgery by Alexis Carrel and Emerich Ullmann; the former pioneered both vascular anastomosis and its use in organ transplantation, the latter performed the first technically successful kidney auto- and xenotransplantations in dog and goat in 1902 (Barker and Markmann 2013). The first human kidney transplantation was conducted by Yurii Voronoy in 1933. The kidney from a deceased donor stopped functioning, as well as four other homografts performed by Voronoy later. Mechanisms of rejection were almost not understood at that time and, therefore, no anti-rejection therapy was available.

Leo Loeb recognized the role of lymphocytes in graft rejection in 1945, starting with the publication of his finding a vast field of transplant immunology (Loeb 1945). However, the report was accepted with scepticism, and the idea of cellular rejection was dismissed for years, until the publication of the work of Rupert Billingham, Leslie Brent and Paul Medawar in 1953 (Billingham et al. 1953). Allograft rejection was shown to be prevented by chimerism induction; also the role of cellular rejection was recognized.

A very elegant way of overcoming rejection problem was chosen by Joseph Murray for his famous living donor kidney transplantation performed in 1954 in Boston. He used the patient's identical twin as the donor of a kidney transplant (Murray et al. 1955).

During the next years lethal total body irradiation (TBI) in combination with inoculation of donor bone marrow cells (strategy developed by Joan Main and Richmond Prehn) was used for the induction of chimerism by Murray's team – with disappointing outcome: all but one graft recipients who received TBI died within one month (Murray et al. 1962). Jean Hamburger and René Küss showed later that the immunosuppression alone, without the induction of chimerism was successful by performing a series of kidney transplants in non-twin patients, preconditioned by TBI (Küss et al. 1962). One more important step was made by Roy Calne in 1960, who showed that 6-mercaptopurine and its derivative azathioprine

could successfully prevent rejection when used instead of TBI (Calne 1960). Finally, Thomas Starzl during 1962-1963 developed the first modern-day immunosuppressive protocol that consisted of prednisone and azathioprine; it allowed >70% 1-year kidney graft survival. This breakthrough can be seen as the beginning of modern era of organ transplantation (Starzl 1990). The main landmarks of this still ongoing period are the development of techniques for transplantation of nonrenal organs (heart, lung, liver, pancreas) and the improvement of immunosuppressive regimens. Thus, the replacement of azathioprine by the fungal derivative cyclosporine dramatically improved outcomes of kidney transplants (Starzl et al. 1980). Later, in 1989, an even more potent immunosuppressive drug, tacrolimus, has become a baseline immunosuppressive agent (Starzl et al. 1989). Modern immunosuppression regimens with cyclosporine or tacrolimus, prednisone and T-cell antibodies allow excellent short- and midterm survival of allografts. However, such problems as immunosuppressive drug toxicity and organ failure due to chronic rejection are still waiting for solutions.

It can be clearly seen from this short historical overview that transplantation is situated at the crossroads of different areas of medicine. The publications presented in the thesis are devoted to the investigation of some interdisciplinary aspects of simultaneous pancreas-kidney transplantation and living donor kidney transplantation.

The aim of the study presented in the first publication was the assessment of incidence and indications of, and the short- and long-term outcomes after a surgical salvage-procedure called “enteric conversion” (EC), which was performed in a group of recipients of simultaneous pancreas-kidney transplants (SPK) at the Department of General-, Visceral-, Vascular- and Transplant surgery of the hospital of the Ludwig-Maximilians-University Munich (Kleespies et al. 2011). SPK, first performed in 1966 by William Kelly and Richard Lillehei (Kelly et al. 1967), is an established therapy for diabetic patients with end-stage renal failure. It can be considered the most effective way to achieve stable insulin secretion and kidney function and, as a result, is able to stabilize or even improve diabetic complications (Jiang et al. 2014). Enteric drainage of the pancreatic juice (ED) is the most physiological and nowadays preferred method for the management of exogenous pancreatic secretions. Several other surgical techniques were quite successfully applied for this purpose at different time periods, as reported in the literature (Bloom et al. 1997, Cattral et al. 2000, Gruessner et al. 2008, Monroy-Cuadros et al. 2006, Stratta et al. 1997, Sutherland et al. 2001). Different techniques of pancreatic drainage were also in use at the hospital of the

Ludwig-Maximilians-University. Thus, the prolamine duct occlusion technique, where alcoholic solution of aminoacids was injected into the pancreatic duct for its complete mechanical obstruction (Land and Weitz 1979), was used in 95 distal pancreatic transplants, performed between 1979 and 1989 (Illner et al. 1988, Illner et al. 1991). Bladder drainage (BD) was used in 121 whole pancreaticoduodenal transplants, performed between 1989 and 2001 (Abendroth et al. 1992, Illner et al. 1995). In this technique, pancreaticoduodenal graft was placed extraperitoneally, with the establishment of anastomosis of the duodenal graft to the urinary bladder, thus providing direct bladder drainage of exocrine pancreatic secretions. Although BD technique possessed significant advantages with respect to the pancreatic graft monitoring (monitoring of rejection by urine amylase measurement; performing of cystoscopic visualization and biopsies of the pancreatic graft), it also carried the risk of development of a unique set of long-term complications, related to continuous irritation of the urinary bladder by exocrine pancreatic secretions, e. g. bleeding, urinary tract infections, graft pyelonephritis etc. (Sollinger et al. 1992, Sollinger et al. 1993). In case of severe, conservatively not manageable complications, EC procedure had to be performed with the intention to preserve the pancreatic graft. In our study, EC was performed in 32 patients (26.5% of all BD patients), with the following main indications: genitourinary complications (62.5%), duodenal graft complications (15.6%), graft pancreatitis (12.5%), graft pyelonephritis (6.3%) and metabolic acidosis (3.1%). Briefly, surgical procedure of EC consisted of separation of the duodenocystostomy with the subsequent closure of the urinary bladder and a side-to-side duodenojejunosomy in most patients or Roux-en-Y reconstruction. Short-time postoperative surgical and general complications occurred in 10 (31.3%) and 13 (40.6%) patients, respectively. Nevertheless, long-term results after EC were excellent (median postoperative follow-up was 8.8 years): patient and pancreatic allograft survival rates were 93.8%, 90.6%, and 71.9% at 1, 5, and 10 years, and 87.5%, 75.0%, and 68.8% at 1, 5, and 10 years after EC, respectively. Therefore, the rates were comparable to those SPK recipients with primary ED. A special survey, completed by all 21 EC patients who were alive at the time of the analysis, demonstrated a high level of satisfaction of patients with the outcome of the procedure. Thus, preoperative symptoms resolved completely or at least significantly in all patients. Patients agreed that EC was necessary to control their BD-associated symptoms, which were rated as severe by the majority of patients. Additionally we performed a comparison of several remarkable retrospective EC studies, since no articles with systematic analysis of EC were available at the time of publication. We found that EC was performed in 12% to 26% (39.5% in one study (Bogetti

et al. 2004)) of BD patients, because of four main groups of indications: genitourinary symptoms, late graft pancreatitis, metabolic acidosis and complications of duodenal segment; early postoperative course seemed to be complicated in majority of patients, with postoperative leakage as a major surgical complication in 8-20% patients (Black et al. 2003, Bogetti et al. 2004, Connolly et al. 2001, Fernandez-Cruz et al. 1997, Jiménez-Romero et al. 2009, Perosa et al. 2004, Sindhi et al. 1997, Van der Werf et al. 1998, West et al. 1998). To the best of our knowledge, our study demonstrated the largest EC experience outside the US with the longest follow-up (106 months post-EC). It showed, that enteric conversion procedure could be performed with excellent results even many years after the initial simultaneous pancreas-kidney transplantation and will be followed by resolution of BD-associated symptoms. We can further conclude that with the advance of surgical techniques, the quality of organ transplants, performed in outdated techniques even many years ago, can be successfully improved. As a result, the quality of life of transplant patients can be increased dramatically.

In the second study, presented in this thesis, we analyzed the influence of some aspects of the lunar cycle on perioperative and long-term outcomes after living donor kidney transplantation (LDKT) (Kleespies et al. 2017). As mentioned before, the first successful kidney transplantation was a LDKT on identical twins, performed by Joseph Murray in 1954 (Barker and Markmann 2013). Because of several non-immunological factors, such as shorter cold ischemic time for donor organ, shorter time for the recipient spent on a waiting list, the possibility of specific donor and recipient conditioning and flexibility in scheduling of timepoints of surgery, LDKT, in comparison to deceased donor transplantation, provides better outcomes for both patient and graft survival (Davis and Delmonico 2005, Magee and Pascual 2004). However, LDKT is also a type of surgical procedure where strong emotions such as fear and hopes are typically present. Since the German Transplant Act (TPG) allows living donation of non-regenerative organs only to relatives of the first or second degree, spouses, registered life partners or other persons with whom the donor obviously has a very close personal relationship (§ 8 para. 1 no. 4 TPG), a strong emotional connection frequently exists between donor and recipient. Positive feelings that arise from decisions to donate and to accept an organ can improve the well-being of both donor and recipient (De Groot et al 2012, Gillil and Lowes 2008, Pradel et al. 2003, Waterman et al. 2006). However, the level of negative emotions can also be quite high, especially when complications occur. Therefore, a strong wish to avoid any kind of complication is very typical, and it is not uncommon, that patients and/or their relatives try to choose a date of LDKT surgery, using superstition-based

predictions. A widespread superstition is, that the lunar cycle might influence the course of diseases, and up to 10,5% (17.5% in the southern part) of German population believes in it (Holzheimer et al. 2003). This old concept, possibly based on the works of Galen and Hippocrates, almost completely lost its credibility after 1700, since it was incompatible with emerging empirical science (Harrison 2000). After the report of an US surgeon EJ Andrews, who observed an increased incidence of bleeding complications after tonsillectomies performed at the full moon (Andrews 1960), the moon phase hypothesis again gained attention of scientists and lay people in the second half of the 20<sup>th</sup> century. Since then, a rising number of articles in supporting or disproving the moon phase hypothesis were published. Several studies demonstrated significant influence of the moon cycle on such aspects of daily life as alcohol and meal intake (de Castro and Pearcey 1995), traffic accidents (Alonso 1993), crime (Thakur and Sharma 1984), suicides (Jones and Jones 1977) and birth rates (Arliss et al. 2005). Moreover, also some medical events such as general practice consultation rates (Neal and Colledge 2000), hospital admission rates for anxiety and depression (Wilkinson et al. 1997), gastrointestinal bleeding rates (Román et al. 2004), atrial fibrillation rates (Mikulecky et al. 1996) and myocardial infarction rates (Sha et al. 1989) were described to vary throughout the lunar cycle. On the other hand, a number of studies analyzed incidence and outcomes of cardiopulmonary resuscitations (Alves et al. 2003), occurrence of myocardial infarction (Wende et al. 2013), postoperative outcomes of elective ambulatory operations (Holzheimer et al. 2003), surgery for lung (Kuehnl et al. 2008), bladder (May et al. 2007) and breast cancer (Peters-Engl et al. 2001), as well as frequency of emergency operations and intraoperative blood loss after general, visceral, or vascular surgery (Schuld et al. 2011), and could not show a significant correlation to the moon phases. Because of an increasing patient demand for moon phase-adjusted transplant appointments we decided to conduct a retrospective study of a possible clinical impact of the lunar cycle (the moon phase and the position of the moon in the zodiac) on outcome after LDKT at the Department of General-, Visceral-, Vascular- and Transplant surgery of the hospital of the Ludwig-Maximilians-University Munich (Kleespies et al. 2017). We therefore evaluated 278 consecutive pairs of LDKT donors and recipients with prospectively registered perioperative data, who were operated between 1994 and 2009. Among donors, only three Grade III complications occurred (Clavien-Dindo classification), requiring one surgical and two radiologic interventions. Thus, no further statistical analysis of donor outcomes was performed. The median age of recipients was 42 years. All dates of LDKT surgeries were retrospectively assigned to four main moon phases using StarDate Online

(online service of the University of Texas McDonald Observatory, available from: <http://stardate.org/nightsky/moon>). Thus, 33, 111, 32 and 102 patients were operated during the new, waxing, full and waning moon, respectively. Additionally we determined different moon signs (positions of the moon in the zodiac at the time of the event) for all LDKT dates. According to the concepts of medical astrology, each organ or body part is related to the particular sign of the zodiac and is believed to be under its influence (Papathanassiou 1999). The most relevant moon sign for our analysis was Libra (Balance), since it is associated with kidneys. 17 LDKT surgeries were performed during the moon sign of Libra. Short- and long-term outcome of LDKT was the following: postoperative surgical complications occurred at 59 (21.2%) patients and 26 (9.4%) patients demonstrated delayed graft function. 4 kidney allografts were lost within 30 days after transplantation. Patient and kidney allograft survival rates at 1, 5 and 10 years after LDKT were 98.9%, 92%, and 88.7%, and 97.4%, 91.6%, and 80.6%, respectively. With regard to our main question, no statistically significant differences were observed among patient groups. Thus, with our study we were able to debunk the moon phase hypothesis for LDKT surgery. From a clinical point of view, the results of the study can help to relieve anxiety in those patients and their relatives, who believe in a negative influence of a particular moon phase on the outcome of living donor kidney transplantation surgery. However, the patients, who strongly believe in the impact of the moon phases on the outcome of surgery, should be taken seriously, and the appropriate timing of transplantation should be provided as long as it does not interfere with evidence-based treatment protocols and clinic-specific routines.

Organ transplantation is undoubtedly one of the most interdisciplinary areas of medicine and, therefore, one of the most complicated and challenging. Short- and long-term outcomes of transplantation procedure, graft functioning and quality of life of transplant patient depend on numerous aspects: surgical, immunological, psychological and many others. Although being of different nature, they are equally important and deserve researchers' attention and intensive investigation. Some of these aspects were investigated in two studies presented in this doctoral thesis. Available for researchers and clinicians, the results of both studies will hopefully contribute to further improvement of organ transplantation.

#### 4. Publication 1

Kleespies A, Mikhailov M, Khalil PN, Preissler G, Rentsch M, Arbogast H, Illner WD, Bruns CJ, Jauch KW, Angele MK. Enteric conversion after pancreatic transplantation: resolution of symptoms and long-term results. *Clin Transplant* 2011;25:549-60.

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## 5. Publication 2

Kleespies A\*, Mikhailov M\*, Khalil PN, Pratschke S, Khandoga A, Stangl M, Illner WD, Angele MK, Jauch KW, Guba M, Werner J, Rentsch M. Moon phases and moon signs do not influence morbidity, mortality and long-term survival, after living donor kidney transplantation. *BMC Complement Altern Med* 2017;17(1):440

\*Equal contributors

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\*Equal contributors

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