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Review

Kidney transplantation in an aged patient with multiple comorbidities: A review based on unusual clinical case

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The article raises a question about the possible and effective kidney transplantation in elderly patients with various severe comorbidities. The analysis is based on an example of successful kidney transplantation from a deceased donor when a 67-year-old patient had severe concomitant background: obesity, diabetes mellitus, and cardiovascular disturbances. Despite unfavorable prognosis and further unpredictable illnesses such as COVID-19, candidal esophagitis, coronary attack, and pneumonia, the patient has not develop graft injury or rejection and kept sufficient kidney function.

The research was mainly focused on coexisting illnesses and their influence on kidney transplantation consequences. Following disease groups were discussed regarding their impact on transplantation outcomes and prognosis: arterial hypertension, cardiac disorders, diabetes mellitus, and obesity. Patient's age, previous interventions, and comorbidities were observed for association with outcomes and risk of graft rejection. A review of available publications compared approaches for recipient selection in different clinical centers as well.

Keywords: Kidney transplantation, comorbidity, graft rejection, contraindications for kidney transplantation.

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Introduction

One of the most important achievements of modern medicine is the active development of transplantation. This is a unique part of the medical industry that requires resources for patient treatment, complex staff efforts, enormous material supplementation, and an additional element — a donor's organ or tissue. At the current stage of transplantology evolvement, we can receive grafts from deceased or living donors [1]. Nowadays, human organ and tissue transplantations are effective and life-saving procedures. It is used in cases where other treatments failed to improve the condition, however, the patient has the potential for further healthy activity [2]. Modern transplantology can be considered as an indicator of health care level in a particular country, and as a degree of civilization, society, and humanity. Over the past few years, Ukraine has made a huge breakthrough in the field of transplantation. The number of organ transplants increases every year. This breakthrough became possible in 2019 when the Ukrainian Law "On the use of transplantation of anatomical materials to humans" was adopted by the Government in 2018 to replace the previous law "On transplantation of organs and other anatomical materials to humans", which was adopted in 1999 and expired on January 1, 2019) [3]. In 2021, Ukrainian doctors performed 313 organ transplantations, the highest number ever: 229 kidneys, 50 livers, and 32 hearts were transplanted.

Within the mentioned period, the first time in Ukraine pediatric heart transplantation was performed. The first lung transplantation and synchronous heart and kidney transplantation were performed as well. Today, despite the hard times of martial law, Ukrainian doctors continue successfully transplanting organs and rescuing people. The most widespread type of transplantation is kidney transplantation. On average, two kidney transplantations are performed in our clinic per week, mainly from living family donors. Unfortunately, because of incompatibility, it is not always possible to perform a family kidney transplantation. Those candidates become "waitlisted" for a long time, expecting desired kidney graft, which would be immunologically compatible [4]. However, not only the ABO blood type is crucial in resolving the issue of transplantation, but many other aspects play a role in compatibility.

From 5 to 7% of the population in Europe live with CKD stage 1, and an additional 4.6% of Europeans suffer from stage 3 or 4 [5]. Today, end-stage kidney disease (ESRD) is a cornerstone of indication for kidney transplantation and is assessed by the glomerular filtration rate (GFR) based on serum creatinine levels. In most cases, patients with GFR values of 15–30 ml/min belong to the severe stage, and GFR values <15 ml/min reflect the terminal stage of ESRD [6]. It may mistakenly seem that these indications are an indisputable rule for kidney transplantation, but it should be noted that contraindications to kidney transplantation exist as well. There is a list of absolute and relative contraindications for kidney transplantation, which is mainly divided into absolute and relative.

Absolute contraindications:

AIDS;

Active malignancy;

Irreversible organ failure;

Inability to tolerate surgery.

Relative contraindications:

Active infections: oropharynx, respiratory system, urinary tract, etc.;

Severe cardiac or pulmonary disease;

Drug/alcohol abuse;

Diabetes mellitus;

Uncontrolled psychiatric disease

Obesity (BMI – 35 kg/m2 and above) [7, 8].

Apparently, young to middle-aged recipients without severe comorbidities demonstrate better outcomes and develop a lower risk of postoperative complications. From time to time, publications describe clinical cases of successful kidney transplantation in aged patients with severe comorbidities [9–11], indicating the probability of ensuring a better of life quality for those selected patients, although the presence of negative comorbidities usually predisposes to poor prognosis.

Here is an example of successful kidney transplantation with a graft from a deceased donor. The patient had several comorbidities, which were relative contraindications: chronic cardiovascular insufficiency, diabetes mellitus type II, and grade II obesity. It should be noted that besides comorbidities, within a year after kidney transplantation, the patient suffered from a few serious diseases which harmed the transplanted kidney and posed a direct threat to the patient's life, but did not lead to transplant rejection or graft function loss. This case indicates a wider opportunity for successful kidney transplantation, especially in patients with severe comorbidities. To confirm this fact, we present the patient's disease timeline.

Case report

Patient K., 67 years old, was diagnosed with coronary artery disease (CAD), atrial fibrillation; arterial hypertension, NYHA 2, diabetes mellitus type II complicated with nephropathy, nephrosclerosis, ESRD 5 stage; diabetic retinopathy; stage II obesity. The patient has been receiving programmed hemodialysis for 5 years, 12 hours a week (average creatinine ranged from 550–600 μmol/l decreased after hemodialysis to 150–170 μmol/l). The patient has been placed on a waiting list for 5 years before undergoing kidney transplantation.

In July 2019 (almost 1 year before kidney transplantation) patient was urgently hospitalized in the ICU department with a serious condition of the acute coronary syndrome, NYHA, stage II B (ejection fraction 60%), bilateral pleural effusion, and the above-mentioned comorbidities. Urgent coronary angiography was performed, during which hemodynamically significant stenosis (50%) of the two main coronary branches was confirmed and resolved with eluting stent placement. After a successful intervention, the patient was managed in the ICU, and his condition gradually improved: chest pains disappeared, increased tolerance to exercise, and due to an increase in serum creatinine to 450 μmol/l hemodialysis was performed out of turn. So, the patient was discharged from the hospital soon with appropriate recommendations.

After 5 years on a waiting list, in March 2020, he underwent successful kidney transplantation with a graft from a deceased donor. Following immunosuppressive regimen: advagraf (5 mg) and methylprednisolone (4 mg) daily. After surgery, the patient's condition improved significantly, no acute renal rejection was observed, serum creatinine decreased to 117 μmol/l, and blood pressure stabilized as well.

In September 2020, the patient was rushed to a surgical hospital with complaints of severe abdominal pain, nausea, and acute kidney rejection was suspected. Upper endoscopy showed erosive gastritis (no evidence of bleeding), and severe candidal esophagitis. Renal rejection was not confirmed and serum creatinine did not rise above 110 μmol/l during the hospital stay.

The next patient admission took place in May 2021 due to acute COVID-19 complicated by bilateral pneumonia. The patient was placed in the ICU with oxygen supplementation. It should be noted that despite the patient's severe condition, the presence of anemia, leukocytosis, and high serum glucose, serum creatinine level did not exceed 144 μmol/l, which indicated the preserved function of the transplanted kidney and no significant impact on the underlying disease. Intensive care resuscitation was prescribed, which proved to be effective, and allowed for discharging the patient from the hospital in a satisfactory condition.

Six months later, in December 2021, the patient was urgently admitted to the emergency again with complaints of constant lower abdomen pain, bloating, fever up to 39 C, headache, and moderate nausea. Signs of graft rejection of the transplanted kidney are suspected. The patient was consulted by a transplantologist, who conducted several

clinical studies: CBC, urinalysis, blood biochemistry, and ultrasonography. But there were no special findings or markers of kidney graft rejection, the level of diuresis was sufficient and serum creatinine was 103 μmol/l, which indicated preserved graft function. So, the diagnosis of kidney transplant rejection was not confirmed. The patient was hospitalized in a surgical department, and after a comprehensive investigation, a diagnosis of bowel indigestion was made. The patient was discharged after 5 days in satisfactory condition.

The next patient's admission happened in March 2022, when he was taken to the cardiology department of the First Medical Department of Lviv with signs of an acute coronary event and complaints of severe general weakness, dizziness, and shortness of breath. After resolving coronary artery disorder, additional examination revealed acute right-sided pneumonia, so the patient was transferred to the pulmonary center of the First Medical Department of Lviv. And again, comprehensive lab tests, imaging studies, and consultations didn't prove kidney graft rejection. At the time of admission, serum creatinine level didn't exceed 142 μmol/l.

The clinical case described above is of great interest, mainly due to the multiple risk factors present, which are associated with worse outcomes of kidney transplantation. As widely known, arterial hypertension, coronary artery disease, overweight, diabetes and advanced age in candidates for kidney transplantation are factors that worsen the prognosis of the transplant procedure and increase the frequency of its early and late complications.

Regarding the post-transplantation period course, the factors listed above, as well as infectious complications, COVID-19, and anemia – negatively affect graft functioning and increase the risk of rejection. In general, the listed risks also increase mortality.

Issues of kidney failure and patients' management after transplantation are quite widespread and relevant. Active discussions about risk factors and principles of recipient selection for transplantation are ongoing. Based on the given clinical case, our team decided to consider the impact of each risk factor on these problems and analyze current recommendations and guidelines.

Research strategy

The main research purpose of the available documents was to compare this case's peculiarities with the latest trends in world medicine. A comprehensive analysis of the published literature over the past years was performed. The research was done in a database of medical publications MEDLINE and PubMed, both from 2012 to 2022. The following MeSH terms were used to conduct research: "kidney transplantation", "graft rejection", "comorbidity", "risk factors", "COVID-19", "heart diseases", "diabetes mellitus", "aged", and "contraindications". We included only available full-text sources in the final review. Clinical cases, review articles, and meta-analyses were involved in the analysis. A total score of 15,862 publications was found in the MEDLINE and PubMed publication databases during the specified period, including 578 full-text sources; 24 sources were selected because of their close relation to the current problem. Discussion issues corresponded to our clinical case, namely kidney transplantation in the elderly, with cardiac pathology, diabetes, and morbid obesity; attention was also paid to publications about comorbidities, specific infections and COVID-19 disease in patients after kidney transplantation, the incidence and features of transplant rejection.

Hypertension and Other Cardiac Disorders

The main independent risk for acute cardiovascular diseases (CVD) after successful kidney transplantation is preexisting arterial hypertension. At the same time, this risk factor is the most common too. More than 50% of kidney recipients at the stage of ESRD are present with elevated blood pressure, and arterial hypertension remains after successful transplantation in the majority of patients [5]. CVD is likely to happen in the early period after transplantation among hypertensive recipients. The same sources reported that up to 40% of all recipients experience CVD in the first 3 years. As mentioned above, because of the common reasons for post-transplantation CVD, arterial hypertension has to be controlled and treated aggressively [5].

CVD is a leading reason of potential mortality in both kidney recipients and patients who receive renal replacement therapy [12,13]. The overall presence of coronary artery diseases (CAD) increases mortality risk more than twice and CVD as part of mortality after kidney transplantation exceeds 30% [13,14]. Despite this statement, there is no clear understanding of the recipient follow-up strategy and cardiovascular evaluation of potential kidney graft recipients remains controversial [14]. Today, electrocardiography is used mainly for screening and selecting patients for other, more efficient invasive investigations. Unfortunately, routine cardiac evaluation is usually not performed for asymptomatic patients although known risk factors for patients with ESRD are the age

of over 45 years, arterial hypertension, dyslipidemia, diabetes, history of smoking, and peripheral vascular diseases [12]. So, it makes sense to expand cardiac evaluation among high-risk candidates and recipients of kidney transplantation [12].

Finally, Malyszko et al reported that potential recipients with CAD were withdrawn from the waiting list even after successful revascularization. US colleges, Concepcion et al. presented a similar statement that patients with renal failure and CAD not acceptable for revascularization are reasonably excluded from the waiting list. Furthermore, some centers exclude 60-year-old patients with ESRD from the waiting list with evidence of CAD or peripheral artery diseases, or both [13,15].

Local recommendations, published by the State Institution "Institute of Nephrology of the NAMS of Ukraine", do not exclude from the waiting list patients with ESRD after successful coronary revascularization, but only advise CAD follow-up annually. In general, there are no controversies in the described clinical case. Some transplant centers interpret and see this case as one with relative contraindications to transplantation. Local recommendations, on the other hand, do not exclude the possibility of transplantation, and only insist on a more thorough examination of the potential recipient with CAD after revascularization.

Obesity

Overall obesity prevalence among adults is high. Di Cocco et al reported in 2016 that up to 2 billion adults were overweight and more than 600 million were obese. Obesity developed a worldwide epidemic character. The total overweight rate is about 35% for men and 40% for women. It is known that final treatment outcomes may depend on the patient's weight. Moreover, obesity is associated with hypertension, hyperlipidemia, CVD, and diabetes in the general population. So, the higher the BMI is, the higher the complication frequency and the worse results. Chan and colleagues reported that there was a strong relationship between recipient obesity and delayed kidney graft function with subsequent gradual graft failure. Lower patient- and graft survival rates are the consequences of preexisting obesity. It has been shown that obesity in renal transplant recipients is also related to CVD mortality, and congestive heart failure [16]. According to different sources, obese kidney transplant recipients had an HR of patient death of about 1.2, and allograft loss in obese recipients was 1.5 times higher than in kidney recipients with a normal weight [17].

There are more controversies among official organizations about contraindications to kidney transplantation because of excessive patient weight. Some transplant hospital centers in USA and UK exclude potential recipients from a waiting list for kidney transplantation if the patient's BMI exceeds 35 kg/m^2, and it's about 10% of the total exclusion [16]. On the other hand, the European Association of urologists proved that kidney transplantation brings higher survival rates and better quality of life in obese recipients. Regardless of no evidence based on BMI, many centers still use obesity as a contraindication for kidney transplantation [18,19]. Despite no clear position about contraindications in recipients with BMI above 35 kg/m^2, there is strong evidence of the relationship between obesity and transplantation outcomes. The British Transplant Society affirmed that obesity (BMI>30 kg/m^2) causes procedural difficulties and increases the risk of complications, and a BMI of >40 kg/m^2 does not bring advantages from kidney transplantation compared to dialysis [18,20]. Many US programs of kidney transplantation consider a BMI above 35 kg/m^2 to be a relative contraindication.

Finally, Costas F. from Greece summarized in a review that an absolute contraindication to kidney transplantation is only BMI higher than 40 kg/m^2, but BMI below 35 kg/m^2 is a relative contraindication for both isolated kidney and complex kidney-pancreas transplantation mainly due to surgical complications.

We didn't find references to local guidelines or protocols regarding the impact of being overweight on patient selection and outcomes for kidney transplantation. Obviously, in this issue, Ukrainian transplant centers rely on foreign sources.

Diabetes

Diabetic nephropathy timely leads to ESRD and is a common reason for kidney transplantation. Both types of diabetes mellitus can cause renal failure, and in both cases, kidney transplantation is an option. Life expectancy was higher for younger recipients with diabetes type (average gain of 17 years), whereas the advantages were significant even for patients with diabetes type 2 older than 60. It is worth referring the diabetic patient with ESRD to the transplant center early when GFR is above 25 mL/min because preemptive kidney transplantation shows a significant survival advantage [20]. A few decades ago, kidney transplantation, caused by both types of diabetic

nephropathy was associated with increased cardiovascular and infectious complication rates, and as a result – high mortality. In those times, kidney transplantation was considered a relative contraindication in patients with diabetes mellitus. Hyperglycemia is associated with worse outcomes and causes diabetic nephropathy de novo, so successful kidney transplantation should be kept with intensive glycemic control [20]. Regarding diabetes mellitus, in the context of influencing outcomes and selecting candidates for kidney transplantation, we were unable to find published guidelines from Ukrainian transplant centers. There are also no generally accepted guidelines for the management of such patients after a successful surgery.

Age

The recipient's age is a strong, independent risk factor in the case of kidney transplantation. At this time, aged patients (65+) exceed 40% of all ESRD population, and this percentage is growing further [15,21]. Among aged recipients, the most common cause of delayed allograft loss is a patient's death with a remained kidney function, which is found in 42.5% of all cases of graft loss. When compared, recipients older than 65 have a seven times higher risk of death with preserved kidney function than young adults [21]. However, kidney transplantation is a safe treatment for selected elderly patients with ESRD aged even over 70. And the cornerstone of the problem is low adherence rather than recipient age [22]. Altogether, aged recipients demonstrate a decreased risk of graft rejection, but they have a higher risk of death related to rejection than younger patients [23]. In contrast, cases with a donor aged over 50 are associated with an increased risk of rejection [21]. On the whole, aged recipients show decreased frequency of kidney graft rejection but have a higher prevalence of infectious and malignant complications [23].

In summary, Hernandes et al announced that elderly patients with ESRD, who are placed on the waiting list of low-risk candidates, could be selected for kidney transplantation. The advanced age of the recipient shouldn't be a strict contraindication and kidney transplantation may offer much better outcomes than dialysis, even in senior age. The same trend can be found in a review by Concepcion and colleagues, where they conclude a statement of absent clinical criteria that make advanced age only a contraindication for kidney transplantation. Promising results come from Eurotransplant Senior Program, where donor kidneys aged more than 65 are preferably assigned to aged recipients, with perspective mid-term outcomes [25]. Summarizing what has been described about the recipient's age, currently, there is no exact threshold regarding the patient's age as excluding factor. On another hand, aged patients are more likely to face complications in the procedure of kidney transplantation.

Rejection Risk

Recipients after kidney transplantation can potentially develop different complications. The major focus of follow-up is to reveal and prevent graft rejection. Many conditions and states have an impact on rejection occurrence: advanced age, obesity, comorbidities, dialysis history, and repeated transplantation. These recipient-associated risk factors increase the likelihood of kidney graft loss because of rejection [22]. According to available sources, acute rejection occurs in almost 30% of grafts, with two or more above risk factors [26].

In their review, H. Ekberg et al added to the rejection risk factor list donor's age over 60 years, the donor's female sex, and the long ischemia period. Besides compatibility and comorbidity, non-adherence plays a role in post-transplant outcomes. It has a dramatic influence on kidney transplantation outcomes in terms of rejection, graft loss, and increased recipient mortality [22].

Often, in clinical practice recipients may develop kidney graft malfunction. Different factors may elevate serum creatinine concentration, causing conditions that mimic rejection. Pseudorejection as a term was described in the USA in the late 70s [26] and was defined as increased serum creatinine by more than 25%, but the true rejection wasn't proven. Pseudorejection could be caused by similar reasons: uncontrolled diabetes, urinary tract obstruction, graft lymphocele, arterial stenosis or thrombosis, and "morbus de novo". It's really important to distinguish true rejection from other conditions to avoid overtreatment [26].

COVID – 19

A new viral pandemic did influence all aspects of human life. It caused unprecedented restrictions and a dangerous infection with an overall mortality rate of about 3%. There are many reports about direct injuries to different organs. One of three hospitalized patients with coronavirus disease developed acute kidney injury [28]. Pathophysiological mechanisms may be prerenal (fever, dehydration, GIT symptoms, and hypotension) or renal. Direct kidney injury due to COVID-19 is caused by abnormalities, hypoxia, "cytokine storm", and consequent

hemodynamic disturbances [28,29]. Moosavi et al reported higher mortality and a more severe course of COVID-19 infection among kidney recipients compared to the average population. The review by Chan et al found that the mortality rate among patients with COVID-19 and acute kidney failure is six times higher, compared to patients without kidney injury (OR=9.2). A similar analysis showed kidney injury incidence in deceased patients with the coronavirus disease was more than 15 times greater than in survivors [28]. A review from Israel, by Imam et al, calculated that overall, 19% of infected patients needed ICU, 22% required mechanical ventilation and unfortunately, 19% died. So, these published data may prove the statement that the challenging course of in-hospital COVID-19 infection and acute kidney injury are associated with a significant elevation in the risk of patient death.

Miscellaneous

In general, recipients are always at higher risk of infection due to different factors, like immunosuppressive regimens, preexisting ESRD, and other comorbidities [32]. A constellation of different infections may affect immunocompromised patients, some of them are not frequent to other individuals. Signs of inflammation and fever are diminished in transplant recipients. An immunosuppressive regimen leads to decreased leukocyte counts and diminished temperatures, so often, infections in transplant recipients may appear in the minor laboratory or radiographic findings. More than one-third of recipients' infections have no fever, especially in the case of fungal infections, but more than 20% of cases of fever are noninfectious [33]. Similarly, poor response to infection can be faced against viral infection, such as COVID-19.

Delayed diagnosis and treatment result in increased transplant recipients' mortality associated with infections. The main reasons for higher mortality are immunosuppressive regimen, mixed coinfections, diabetes mellitus, kidney and liver failure, leukopenia, and comorbidities [33]. Candidal esophageal lesions may appear due to immunosuppression, herpes or cytomegalovirus coinfections, and other underlying disorders. Generally, nosocomial infections may have a huge impact on transplant outcomes because of diminished symptoms but higher complication and mortality rates.

Posttransplant anemia is common and may be developed in any period after transplantation with a prevalence of almost 50% of the total kidney recipients. Anemia is responsible for increased graft failure and recipient mortality; both are prominently higher with more severe anemia [34]. Kidney graft function prognosis also depends on hemoglobin level.

Finally, to summarize the main factors that affect transplant results, a review by Concepcion et al, showed almost 20 factors associated with post-transplant results (patient age, different comorbidities, transplantation and hemodialysis history, gender, etc.). Comorbidities play a role in transplant consequences when two or more chronic conditions are present. For a quantitative prognosis, the most commonly used score is Charlson Comorbidity Index (CCI). The higher the CCI score in the kidney transplant recipient, the shorter the life expectancy [15]. By the way, according to CCI calculated retrospectively, this clinical case with multiple comorbidities has a low 10-year survival expectancy at the level of 2% only.

Discussion

This clinical case interested us due to its unusual course and several patients' comorbidities. That case was a challenge in terms of contraindications for kidney transplantation. Deceased-donor kidney transplantation was performed on a patient with a couple of severe comorbidities. A 67 y. o. patient suffered from coronary artery disease (coronary stent placement 2019), atrial fibrillation, complicated course of arterial hypertension, NYHA 2; hypertensive nephropathy, nephrosclerosis, grade 5 ESRD (12-hour hemodialysis sessions per week), type 2 diabetes mellitus, diabetic retinopathy, stage II obesity. There are a few relative contraindications to kidney transplantation, the vast majority of which were observed in this clinical case. Before kidney transplantation, the patient had regular disturbances associated with heart failure, recurrent angina, high arterial pressure, complications of diabetes, and was overweight (BMI 39.8 kg/m2). After all, he was not a typical candidate to obtain a graft. Only the presence of terminal ESRD stage 5 was an absolute indication of kidney transplantation. But constellations of decompensated comorbidities and the risk of possible postoperative complications could offset the benefits of transplantation.

However, despite the high risk of possible postoperative complications, the patient was successfully operated on. As it turned out later, the risk was justified. After successful kidney transplantation, the patient was admitted to

different wards 5 times because of various acute conditions and diseases. Every time, the suspected rejection wasn't confirmed. We deliberately described a timeline of the patient's hospitalizations because of different events to emphasize the variety of pathologies that happened to the patient before and after transplantation. For an immunosuppressed elderly patient with severe comorbidities after kidney transplantation, each of these diseases has a significant negative impact and is life-threatening, especially two episodes of pneumonia (one case caused by COVID-19). First of all, the kidney graft is under threat. Every event could lead to negative consequences up to the rejection of this kidney graft. Upon careful analysis of diseases that the patient suffered from during the year after transplantation, we found a clear trend associated with a significant lack of negative impact on graft function. The analysis of patient records allows us to conclude that there are no significant changes in graft function. The main criteria for quality control of graft function were GFR, and serum creatinine. Among all diseases described, the patient had no signs of renal insufficiency, diuresis was sufficient, and creatinine levels once rose to 144 μmol/l in case of pneumonia caused by COVID-19.

Thus, the described case indicates that despite the huge risk of complications, there is a real opportunity for successful kidney transplantation and its subsequent function in elderly patients with multiple comorbidities. Comprehensive local guidelines and follow-up protocols will help solve controversies and misunderstandings in kidney recipient selection.

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