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Kidney functional changes over time in liver recipients

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Background. *Glomerular filtration rate is the main parameter characterizing the kidney functional condition. The evaluation of glomerular filtration rate is of significant importance, since in addition to an objective indicator of the kidney functional capacity, it is also a predictor of various pathological conditions, including cardiovascular complications.*

The aim *of the study was to assess creatinine levels and glomerular filtration rates before and after orthotopic liver transplantation in clinical practice.*

Material and methods. *A retrospective analysis of data obtained at different stages of the postoperative period in patients (n = 89) who underwent orthotopic liver transplantation in Research Institute – Regional*

Clinical Hospital № 1, Krasnodar, was performed. The creatinine level and glomerular filtration rate were studied before and at 6, 12, 24, and 36 months after liver transplantation, taking into account gender and age differences. Statistical analysis of the study results was made using Statistica 10 software.

Results. *The creatinine level was 82.9 ± 19.8 mmol/L before liver transplantation; creatinine increased by 20.4% (p = 0.004) at 6 months, by 24.8% (p = 0.00001), 24.4% (p = 0.0004), and 26.0% (p = 0.0005) at 12, 24 and 36 months after transplantation, respectively statistical significant in all cases. Compared to the baseline, the glomerular filtration rate decreased by 14.2% (p = 0.0005), 18.8% (p = 0.00001), 20.2% (p = 0.00003), and 22.6% (p = 0.00006) at 6, 12, 24, and 36 months, respectively statistical significant in all cases. Significant differences in kidney functional condition between men and women, as well as between the recipients younger and older 50 years were observed only at one year after transplantation.*

Conclusions. *In the long-term postoperative period, there was an increase in creatinine level and a decrease in the level of glomerular filtration rate compared to the period before liver transplantation. At 6 months, two, and three years after liver transplantation, there were no significant differences in the studied liver functional parameters between the age groups or genders. Monitoring the glomerular filtration rate and preventing the progression of renal dysfunction in liver recipients are necessary regardless of age and gender.*

Keywords: liver transplantation, chronic kidney disease, creatinine, glomerular filtration rate

CKD, chronic kidney disease

GFR, glomerular filtration rate

OLT, orthotopic liver transplantation

Introduction

The introduction of new immunosuppressants, the improvement of surgical techniques, an early detection and treatment of complications provided a significant improvement in the liver recipient survival that reached more than 70% at 10 years after surgery [1, 2]. Late postoperative complications and long-term results become one of the main problems for the attending physicians of the liver transplant recipients. The chronic kidney disease (CKD) is one of the risk factors for poor prognosis. Even a moderate decline in renal function in the general population is known to lead to a significant decrease in life expectancy, worsening of other health parameters, and increased treatment costs [3, 4]. The need for in-hospital treatment in patients with CKD is 38% higher compared with people without CKD. Mortality among CKD patients is 43% higher and is primarily associated with cardiovascular and infectious complications [5]. The main parameter characterizing the kidney functional condition is the glomerular filtration rate (GFR). So the GFR assessment is of significant importance, since, being an objective indicator of the kidney functional capacity, it is also a predictor of various pathological conditions, including cardiovascular complications [6-11].

The study objective was to assess the creatinine level and calculate GFR before and in the long-term after orthotopic liver transplantation (OLT) in clinical practice.

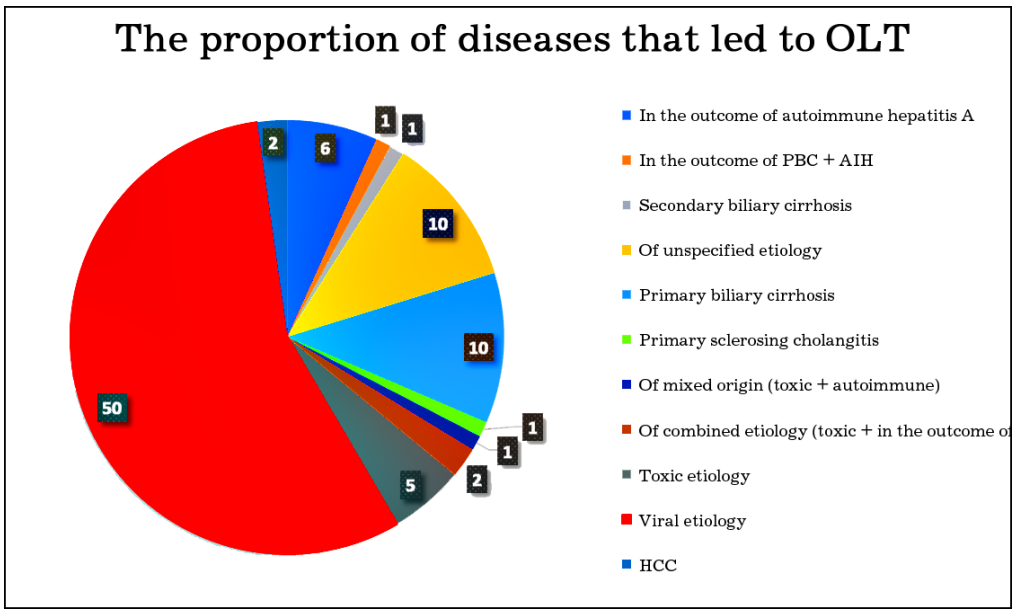
Material and methods

A retrospective data analysis of the patients (n = 89) operated on in the Research Institute–Regional Clinical Hospital No.1 n.a. Prof. S.V. Ochapovsky, Krasnodar. The article presents the assessment of patients' GFR before liver transplantation and at 6, 12, 24, and 36 months after the surgery. The data were retrieved from primary medical records: an Outpatient Medical Record (Form No. 025/y-87), an inpatient medical record (Case History, Form No. 003/y-80). The creatinine and GFR levels were assessed according to the CKD–EPI (Chronic Kidney Disease Epidemiology Collaboration) formula [12]. Statistical processing of the results was made using the Statistica 10 software package. The Kolmogorov–Smirnov test (K–S) was used to test for the normality of the distribution that was additionally refined by using the Shapiro–Wilk test (Sh–W). That resulted in revealing the distribution that was not normal for creatinine (K–S test <0.2, Sh–W test <0.05 in the periods before OLT, at 6, 12, 24, and 36 months after OLT), and the distribution that was normal for GFR (K–C test > 0.2 in all studied periods, Sh–W test > 0.05 in the period before OLT, at 6 and 24 months after OLT). The variables with a normal distribution are presented as mean ± standard deviation (M ± SD). The Mann–Whitney test was used for independent samples, and the Wilcoxon test was used for dependent groups. Differences were considered significant

at p <0.05 (a significance level). When comparing two independent samples with a normal distribution, the unpaired Student's test was used, taking into account the equality of the variances. For pairwise intergroup comparison of two samples with a distribution other than the normal distribution, the Mann– Whitney test (independent samples) was used.

Results

The group for the assessment of creatinine and GFR changes over time at 6, 12, 24, and 36 months after the OLT performed in RI–RCH No.1 included 89 adult patients (52.8% men, and 47.2% women), aged 49.6 ± 9.8 years at the time of surgery (from 19 to 69 years old). In most cases, the end-stage liver disease that predetermined patient's need for a donor organ was caused by: viral infection in 56.2% of cases, primary biliary cirrhosis in 11.2%, autoimmune and toxic hepatitis in 6.7%. In 11.2% of cases, the etiology of the disease that caused severe hepatic failure, was not clarified (Fig. 1).



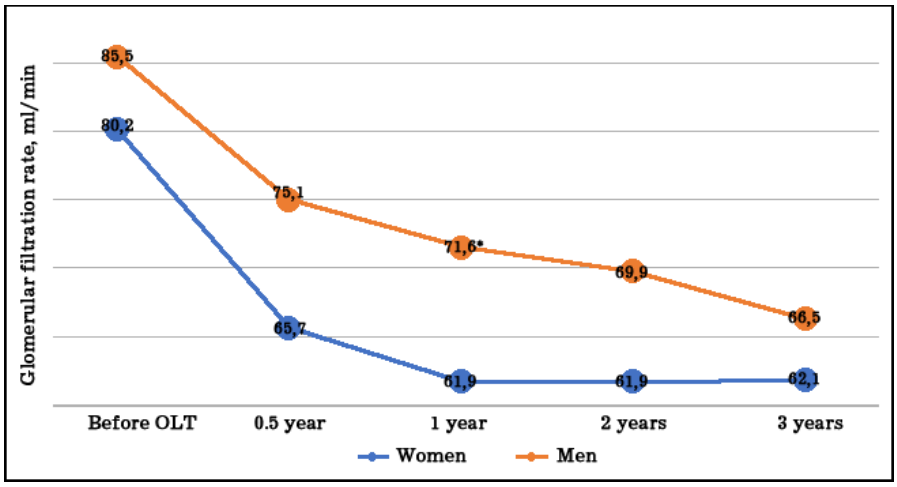
Note: PBC, Primary Biliary Cirrhosis, AIH, Autoimmune Hepatitis, HCC, Hepatocellular Carcinoma

Fig. 1. Distribution of patients with regard to the disease leading to orthotopic liver transplantation

Before transplantation, the blood plasma creatinine was 82.9 ± 19.8 (10.4-787.1) mmol/L; further the blood creatinine level increased by 20.4% (p=0.004), by 24.8% (p=0.00001), 24.4% (p=0.0004), and 26.0% (p = 0.0005) after 6, 12, 24, and 36 months, respectively. The statistical analysis of the creatinine dynamics between the baseline and 6 months after transplantation in women (group 1) revealed no significant differences. In men (group 2), the creatinine level increased as compared to baseline by 15.3% (p = 0.008) after 6 months, by 21.0% (p=0.0003), 19.9% (p=0.0009), and 28.0% (p=0.005) after 12 months, 24 months, and 36 months, respectively. After 12, 24, and 36 months, the increase in creatinine level in the 1st group, as compared to the baseline value, made 24.8% (p=0.005), 22.2% (p=0.017), and 28.7% (p=0.003), respectively.

The GFR was assessed using the creatinine values before liver transplantation, at 6, 12, 24, and 36 months after transplantation. The baseline GFR was 83.4±25.9, the posttransplant GFR was 71.6±21.5 at 6 months after surgery, 67.7±21.6 at 12 months, 61.5±20.5, and 64.6±22.6 after 24, and 36 months, respectively. Thus, the GFR decreased, as compared to the baseline by 14.2% (p=0.0005), 18.8% (p=0.00001), 20.2% (p=0.00003), and 22.6 % (p=0, 00006) after 6, 12, 24, and 36 months, respectively.

The gender-related GFR analysis showed a one-way-directed change with a greater pronounced decrease in GFR in women than in men. In the 1st group, the maximum difference by 22.9% (p = 0.0016) and 22.8% (p = 0.0008) from the baseline value was registered after 12 and 24 months. In men (group 2), the GFR decreased by 16.3% (p=0.00003), and 18.3% (p=0.0013) after 12, and 24 months, respectively. A significant difference between men and women in negative growth was registered only at one year after surgery. At 3 years, the differences in negative dynamics became minimal: GFR decreased as compared to the baseline by 22.3% (p=0.002) in men and by 22.6% (p = 0.001) in women without a significant difference in results with regard to gender (Fig. 2).



* p = 0.001

Fig. 2. Gender differences in the changes of glomerular filtration rate over time after orthotopic liver transplantation

It is interesting to note that the creatinine level increase in our study was less pronounced in the patients aged over 50 years than in younger recipients. Thus, as compared to the baseline, the creatinine level increased in the subgroup under 50 years old by 17.2% (p=0.0123), 32.5% (p=0.0001), 25.1% (p=0.0008), and 24.2% (p=0.0002) after 6, 12, 24, and 36 months, respectively, whereas in the subgroup over 50 years old, the creatinine level increased by 15.99% (p=0.1), 15.99% (p=0.001), 18.2% (p=0.02), and 20.5% (p=0.04), after 6, 12, 24 and 36 months, respectively, as compared to the baseline. However, the assessment of kidney function using the generally accepted GFR formula, which, besides creatinine, takes into account the patient age, showed less pronounced differences. Specifically, as compared to the baseline, the GFR decreased by 13.07% (p=0.009), 19.2% (p=0.000008), 24.3% (p=0.00005) and 24.2% (p=0.00007) after 6, 12, 24, and 36 months, respectively, in the subgroup under 50 years old, whereas in

those over 50 years, there was a decrease in GFR by 15.5% (p=0.03), 17.9% (p=0.002), 16.2% (p=0.007), and 22.7% (p=0.02) after 6, 12, 24 and 36 months, respectively, as compared to baseline. Significant differences between the patients younger and older 50 years in the creatinine increase and GFR decrease were observed only at one year after OLT.

Discussion

CKD is known to develop frequently after OLT [13]. The exact CKD prevalence in liver recipients is difficult to assess because it widely varies depending on the CKD verification method and the duration of follow-up (1–13 years). According to different authors, the incidence of CKD was recorded from 4% [14] to 79% [15]. Such a wide discrepancy, in the opinion of Aisling O'Riordan, Vincent Wong et al [16], is primarily accounted to different CKD assessment methods used over the past decades. It is noteworthy that in the discussions on the appropriateness of using various formulas for calculating GFR, the CKD – EPIC (Chronic Kidney Disease Epidemiology Collaboration) formula was recognized by leading nephrologists in the “KIO 2012 Clinical Practical Guidelines for the Diagnosis and Treatment of Chronic Kidney Disease” as a more prognostic ally valid compared to the Cockcroft–Gault and MDRD formulas [12]. In our study, we analyzed the changes in creatinine level over time, and also evaluated the kidney function in liver transplant recipients, calculating GFR using the CKD – EPI formula based on the aforementioned current KDIGO recommendations [12]. Both the changes in the creatinine level over time and the results of the GFR calculations indicated a decrease in the kidney

function in liver recipients at all stages of follow-up. In the patient distribution by age and gender, the negative trend of GFR changes over time persisted when compared to the baseline value. Similar to our study age gradation in the group of liver recipients, Joelle Guitard et al [17] showed lower GFR in patients over 50 years old compared with patients younger 50 years old. In our series of recipients, the dynamics of renal function decline assessed by GFR values, differed significantly between the age subgroups only at a 1-year time-point after OLT. However, there was a decrease in GFR in the recipients both under and over 50 years in all time-points compared to the baseline values. In their study, John C. La Mattina et al [18] demonstrated an inverse relationship between the liver recipient age and the renal function. The same study emphasized the lack of gender association with the progression of renal function decline, in contrast to the factors of dyslipidemia and pre-transplant diabetes [18]. In our study, there was a greater drop in GFR in women compared to men only at 1 year after the transplant surgery, followed by the continued statistically insignificant trend and almost no gender differences in GFR reduction in all other analyzed periods, including in the most distant period after OLT (3 years). At the same time, a number of authors pointed to a statistically significant association of a female gender with an increased risk of CKD [16, 19–21]. Apparently, the contradictory results obtained in a comparative analysis of the renal failure severity in men and women have been associated with the use of different time frames and methods to assess the renal. Gender differences of kidney damage in liver transplant recipients require their clarification in further well-designed studies. From a practical point,

currently, the most important is the following fact causing no doubt: the liver transplant recipients, both women and men of almost all age groups, experience a kidney function decline as compared to the baseline values.

In general, the authors of major studies who investigated the CKD occurred after OLT [21–24] showed that the renal function impairment is the rule rather than the exception. The causes of CRF developing after OLT include the risk factors both common for general population (arterial hypertension, diabetes mellitus, obesity, atherosclerosis, hyperlipidemia), and specific for liver transplant recipients (chronic HCV infection, previous kidney pathology in liver cirrhosis, and perioperative kidney injury) [13]. The side effects of immunosuppressants, especially calcineurin inhibitors, extremely much contribute to CKD development [19, 21, 25–27]. In the long term, the methods of an immunological tolerance induction are expected to be implemented that would eliminate the need for taking immunosuppressants [28]. By now, the mechanisms of tolerance initiation have been well studied, namely those realized through mesenchymal stem cells and T-regulatory cells, which, unlike T-helper cells, show suppressor activity, suppress the immunity reactions, and determine the development of peripheral tolerance to antigens [29]. Moreover, the methods have been proposed for the immunological tolerance induction in visceral organ transplantation, specifically, through the transfusion of cellular blood components obtained from a post-mortem heart-beating donor [30]. However, in the coming years, these methods will not be implemented everywhere, and in actual clinical practice it is still necessary to take into account that calcium inhibitors are also responsible for more than 70% of

CKD cases after OLT [31]. According to leading experts in transplantation, in CKD it is possible to reduce the doses of calcineurin inhibitors or completely cancel them several months or years after OLT with switching to everolimus as the main immunosuppressant, including in combination with mycophenolates [13]. In order to timely identify CKD, it is important to increase the awareness of doctors responsible for the management of liver transplant recipients about the necessity to monitor GFR and a number of other parameters. The chances of detecting an impaired renal function increase with the increased number of serum creatinine concentration measurements and longer follow-up period [12]. In our study, the medical records contained the data on creatinine level in every study period, so it was possible to retrospectively calculate the GFR value. The introduction of automatic GFR calculation option in laboratories and the inclusion of this parameter, in addition to serum creatinine, in the laboratory test report may be promising. B.R.Hemmelgarn et al noted that such an organizational step had contributed to a 68.4% increase in the primary referral of CKD patients to a nephrologist [32].

Unfortunately, the arsenal of nephrologists and transplantologists has no drugs that would smooth down completely the potential nephrotoxicity of many immunosuppressants. However, experts consider the drug toxicity to be a modifiable factor of CKD and recommend the regular monitoring of GFR, electrolytes and drug concentrations in blood of all patients receiving potentially nephrotoxic drugs, in particular, the attention should be paid, for example, to calcineurin inhibitors, indicating the highest level of evidence-base for this recommendation (1A) [12, 33]. With a timely detection of the

chronic renal dysfunction of any etiology, the patients can be given appropriate recommendations about their physical activity (at least 30 minutes of exercise 5 times a week), achieving a healthy body weight (body mass index of 20-25 kg/m^2), quitting smoking, reducing salt intake to <90 mmol/day (sodium <2 g/day), abstaining form taking herbal medicines. Patients with confirmed CKD need to consult a doctor or pharmacist even before using over-the-counter drugs or protein-containing food supplements (evidence-base, level 1B); herbal medicines are not recommended (evidence-base, level 1B). In patients with CKD, the GFR and the albuminuria level should be assessed at least once a year. GFR and albuminuria should be monitored even more often in patients at a high risk of CKD progression and(or) when measurement results must be taken into account when prescribing therapy, in particular, it is necessary to rely on GFR when choosing the dose of a number of drugs (1A). A timely correction of risk factors requires continuous monitoring of renal function, proteinuria (1B). The treatment of CKD in general population is based on a thorough control of hypertension, and using the blockers of the renin-angiotensin-aldosterone system. The same measures must be effective for liver transplant recipients. According to current recommendations with a high evidence-based level (1A), in patients with the CKD developed in a transplant center setting, the immunosuppression therapy scheme may be switched to a less nephrotoxic one [13].

A significant limitation of our study was its retrospective nature, which did not allow a complete CKD verification due to the fact that the creatinine increase and GFR decrease are of screening nature and cannot be

used to verify CKD without re-monitoring and additional diagnostic tests. Further prospective study with CKD verification to be conducted in accordance with the current requirements of the KDIGO 2012 clinical guidelines seems necessary [12].

The timely verification of CKD, taking the measures to prevent and slow down the progression of kidney function loss, including those through the correction of immunosuppressive schemes, are vital for patients, because with the CKD development the risk of liver recipient's death increases more than 4-fold for a year.

Conclusions

1. In the late postoperative period, a creatinine increase and a glomerular filtration rate decrease were observed in liver transplant recipients, compared to the values taken before liver transplantation.

2. At 6 months, 2, and 3 years after transplantation, there were no significant differences in renal function between the age groups, or between gender-related groups (men vs. women).

3. Monitoring the glomerular filtration rate and preventing the renal dysfunction progression in adult liver transplant recipients are necessary regardless of the age and gender.

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