Original article

Chronic kidney disease after treatment with cyclosporine or tacrolimus in heart transplant recipients – experience of a Romanian medical center

Boala renală cronică la pacienții cu transplant cardiac tratați cu ciclosporină sau tacrolimus – experiența unui centru medical românesc

Mihaela Ispas[1*], Carmen Chincişan[1], Septimiu Voidăzan[2], Alina Mărginean[2], Minodora Dobreanu[2]

1. Emergency Institute of Cardiovascular Diseases and Transplant Târgu Mureş, România
2. Univ Med & Pharm Târgu Mureş, România

Abstract

Renal failure is a complication with prognostic implications in transplant recipients. The aims of our study were to describe renal dysfunction occurring on calcineurin-inhibitor therapies in recipients who underwent heart transplantation at Târgu Mures Cardiovascular Institute between November 1999 and February 2011 and to identify risk factors for decline in renal function. We studied the evolution of renal function in 35 heart transplant recipients in relation to: immunosuppressive therapy (cyclosporine or tacrolimus), gender, age at the time of transplantation, time elapsed after transplantation, diabetes and hypertension. Changes in glomerular filtration rate (GFR) and proportion of patients with a decline in GFR to < 30 ml/min/1.73m^2 from baseline, were analysed at 1, 3, 6 months, and yearly thereafter. Serum creatinine gradually increased post-transplantation in all the recipients; GFR showed a significant decrease from baseline (one month after transplantation) until to fifth year of monitoring, the most significant decrease occurring from one to six months after surgery. After the acute post-transplantation period, heart transplant recipients given long-term treatment with calcineurin-inhibitors experienced only small changes in GFR over time. There were no significant differences in outcome of recipients receiving cyclosporine and those with tacrolimus. Significant chronic decrease in kidney function occurred in 25% of our patients treated with tacrolimus and in 20% of the patients treated with cyclosporine. Increased age at the time of transplantation, the time elapsed since transplant, baseline GFR, hypertension and diabetes mellitus were identified as predictors of renal dysfunction in heart transplanted patients. Survival at five years was similar for the group immunosuppressed with cyclosporine comparative with the group treated with tacrolimus. Conclusion: Treatment with calcineurin inhibitors in heart transplanted recipients is associated with chronic kidney damage. We found a significant decrease of renal function already at six months post transplant, in both immunosuppressive treatments.

Keywords: *heart transplant, post-transplantation renal failure, calcineurin-inhibitors*

[*]**Corresponding author:** Mihaela Ispas, 50 Gh Marinescu Str, Târgu-Mures, 540139, Romania
E-mail: mihaela4@yahoo.com

Rezumat

Insuficienţa renală este o complicaţie majoră cu implicaţii prognostice semnificative la pacienţii transplantaţi cardiac. Obiectivele acestui studiu au fost descrierea disfuncţiei renale apărute consecutiv tratamentului cu inhibitori de calcineurină la pacienţii transplantaţi cardiac între noiembrie 1999 şi februarie 2011, în Institutul de Boli Cardiovasculare Târgu Mureş şi de a identifica factorii de risc pentru declinul funcţiei renale. Am studiat evoluţia funcţiei renale la 35 de pacienţi în raport cu: terapia imunosupresivă administrată (ciclosporină sau tacrolimus), sexul pacientului, vârsta la momentul transplantului, timpul scurs de la transplant, prezenţa diabetului şi/sau a hipertensiunii arteriale. S-au monitorizat modificările RFG estimate (RFGe) după 1, 3, 6 luni şi apoi anual, precum şi proporţia pacienţilor cu o scădere a RFGe sub 30 ml/min/1.73m^2. Concentraţia creatininei serice a crescut progresiv post-transplant la toţi pacienţii; RFGe a înregistrat o scădere statistic semnificativă după prima lună post-transplant şi până în al 5-lea an de monitorizare, cea mai semnificativă scădere fiind înregistrată în intervalul 1-6 luni post-transplant. După perioada acută post-transplant (şase luni post-transplant), pacienţii cărora li s-a administrat tratament cronic cu inhibitori de calcineurină au prezentat modificări minore ale RFGe. Nu am identificat diferenţe semnificative în afectarea funcţiei renale la pacienţii trataţi cu ciclosporină faţă de cei care au primit tacrolimus. O deteriorare semnificativă a funcţiei renale a survenit la 25% din pacienţii trataţi cu tacrolimus, respectiv la 20% din pacienţii trataţi cu ciclosporină. Vârsta înaintată la momentul transplantului, timpul scurs de la transplant, valoarea iniţială a RFGe, hipertensiunea arterială şi diabetul zaharat au fost identificaţi ca predictori ai disfuncţiei renale la pacienţii cu transplant cardiac. Supravieţuirea la cinci ani a fost similară în grupul tratat cu ciclosporină comparativ cu grupul tratat cu tacrolimus. Concluzie: Administrarea inhibitorilor de calcineurină la pacienţii transplantaţi cardiac se asociază cu afectare renală cronică. Am identificat o scădere semnificativă a funcţiei renale, deja la şase luni post-transplant, indiferent de terapia imunosupresoare utilizată.

Cuvinte cheie: *transplant cardiac, inhibitori de calcineurină, insuficienţă renală post-transplant.*

Introduction

The outcome and prognosis of patients with different type of transplants has dramatically improved in the last three decades by the introduction of calcineurin-inhibitor therapy: cyclosporine in 1979 and tacrolimus in 1989, respectively (1, 2). Cyclosporine and tacrolimus are both drugs that arrest cytotoxic T lymphocytes at G0-G1 cell-cycle and produce a dose-dependent inhibition of gene expression for IL-2 and other pro-inflammatory cytokines in helper and cytotoxic T lymphocytes (3).

Renal dysfunction is one of the most important complications that occur after nonrenal organ transplantation and has major consequences on the evolution of these patients (4-6). Renal failure is caused by the nephrotoxic effects of immunosuppressive regimens which produce tubular atrophy, interstitial fibrosis, focal hyalinosis of small renal arteries and chronic glomerular ischemia due to poor renal perfusion. Other causes which can contribute to chronic kidney disease (CKD) in heart transplant receivers are: renal disease before transplantation, increasing age, diabetes mellitus, dyslipidemia and hypertension (7).

The objectives of this study were to emphasize the short-medium and long term evolution of renal function occurring after treatment with cyclosporine or tacrolimus in heart transplant patients and to identify risk factors for decline in renal function.

Material and methods

Study subjects and design

We conducted an observational study on recipients who received orthotopic heart transplant at Institute of Cardiovascular Diseases and Transplantation from Târgu Mures, Romania, between November 1999 and February 2011.

The study group for our analysis contained 43 patients, but only 35 (81.4%) of them survived for more than six months and were included in the study; four of the patients died during the surgical

Table 1. Baseline characteristics of heart transplant recipients in Târgu-Mureş, România, 1999-2011

Characteristics	Recipients (35)
Age - yrs	38 (16 – 59)
Male – no/total	26 / 35
eGFR before transplantation – no (%)	
> 90 ml/min/1.73 m^2	16 (45.7)
60 – 89 ml/min/1.73 m^2	16 (45.7)
30 – 59 ml/min/1.73 m^2	3 (8.6)
Cyclosporine – no (%)	12 (34.3)
Tacrolimus – no (%)	23 (65.7)

intervention and four died less than six months post-transplantation; death for the last group has been caused by other reasons than kidney failure. To assess the effect of heart transplantation and calcineurin-inhibitors exposure on renal function we restricted the analysis to patients who survived at least six months post-transplantation. In order to avoid mingling influence of surgical procedure on renal function, the analysis of renal function began one month after transplantation. All patients received immunosuppressive regimens based on calcineurin-inhibitors: 12 patients transplanted from 1999 to 2004 were treated with cyclosporine and 23 patients patients transplanted after 2004 received tacrolimus, with gradual serum level reduction over time. Patients were followed-up regularly post-transplantation at 1, 3, 6, and 12 months and yearly thereafter, in order to assess their clinical course, namely to detect complications. The mean duration of follow-up was 4 years (3.85 ± 2.86 years).Ten of these patients have been followed for a period of at least 5 years after cardiac transplantation. In all patients the renal function has been monitored: plasma creatinine and urea were measured; estimation of GFR was calculated according to the MDRD - *Modification of Diet in Renal-Disease* formula (8, 9):

$$eGFR\ (ml/min/1.73\ m^2) = 175 \times ({}_{ser}Cr)^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if females})$$

Several parameters were followed for the assessment of renal function evolution: age at transplantation, gender, post-transplant development of diabetes, hypertension, time elapsed from heart transplantation and type of immunosuppressive medication. Mortality during the follow-up was also analyzed.

Statistical analysis

Statistical analysis was performed using SPSS software version 19, GRAPH PAD DEMO and GRAPH PAD PRISM. For univariate analysis of data we used Student's t test for independent variables (continuous variables with normal Kolmogorov-Smirnov distribution), $\chi 2$ test (dichotomous variables), ANOVA test (ordinal dependent variable), and Pearson correlation. Differences were considered statistically significant for a value of $p < 0.05$.

Results

The base-line characteristics of the heart transplant recipients are summarized in *Table 1*.

In the 35 enrolled patients, 26 (74.3 %) were men.The mean age at the time of transplantation was approximately 38 years (16 to 59 years). 23 patients (65.7%) were treated with tacrolimus and 12 (34.3%) with cyclosporine based triple immunosuppressive regimen. Estimated glomerular filtration rate of the group after the acute post-transplantation period (1 month) was 117.1 ± 52.54 ml per minute per 1.73 m^2**.** Coexisting conditions associated with developing kidney disease were

Table 2. Characteristics of patients at 1, 3, 6 months and then at 1 and 5 years after cardiac transplantation[#]

Variable after cardiac transplantation	1 month	3 months	6 months	1 year	3 years	5 years
No. of patients followed-up	35	35	35	32	22	10
Treated with cyclosporine	12	12	12	12	10	6
Treated with tacrolimus	23	23	23	20	12	4
Creatinine (mg/dL) (95% CI)	0.94±0.63 (0.72-1.16)	1.01±0.59 (0.79-1.21)	1.13±0.44 (0.98-1.28)	1.19±0.52 (1.00-1.38)	1.37±0.73 (1.04-1.69)	1.84±1.57 (0.71-2.96)
eGFR (ml/min/1.73m^2) (95% CI)	117.0±52.54 (98.9-135.0)	100.3±45.93 (84.49-116)	80.05±31.22 (69.3-90.7)	82.82±35.18 (70.14-95.5)	75.14±38.07 (58.26-92.02)	61.54±30.60 (39.6-83.4)

[#] Plus–minus values are means ±SD

present before transplantation in a minority of the patients: hypertension in 14 patients (40%), pre-transplant eGFR less than 60 ml/min/1.73m^2 in 3 patients (8.6%). There were no significant differences in characteristics of recipients receiving cyclosporine and those with tacrolimus.

Incidence of chronic renal disease

Serum creatinine gradually increased post-transplantation in all the recipients; the most significant increase occurred from one to six months after surgery. A detailed evolution of serum creatininine concentrations and eGFR, at 1 - 6 months, 1 - 5 years after transplantation are presented in *Table 2*.

In patients with heart-transplant the risk for chronic kidney disease increased over time, with decrease of eGFR in cyclosporine and tacrolimus treated groups (*Figure 1a, b*). GFR fell significantly from one to six months post-transplant (from 117 to 80 ml/min/1.73 m^2) ($p = 0.001$) but thereafter no significant rate of GFR decline has been observed (20 ml/min/1.73 m^2 in 4.5 years). Incidence of chronic kidney disease ranged from 5% at first months after transplantation to 50% at the end of fifth year. Whereas at six months after surgery, an eGFR of 30 ml/min/1.73m^2 was detected in only 1 of 35 patients, at five years 2 of the 10 patients had an eGFR below 30 ml/min/1.73m^2, meaning a significant impairment of the renal function.

Discussion

Immunosuppressive therapy and renal function

All of the 35 surveyed patients received anti-thymocyte globulin as induction immunosuppressive therapy. Maintenance immunosuppressive therapy consisted of chronic administration of cyclosporine for serum levels of 100-200 ng/ml or tacrolimus for serum levels of 5 - 15 ng/ml in chronic regimen.

In many current studies cyclosporine A is considered as the leading cause of renal dysfunction in post-transplant of non-renal organs (10). Cyclosporine nephrotoxicity is due to the renal arteriolar vasoconstriction and, in time, to the development of thickening of the capillary basal membrane, glomerular sclerosis and interstitial fibrosis. In our study treatment with cyclosporine was initiated in 12 post-transplant patients, 11 of them survived after one year and four of them had a reduced glomerular filtration rate (below 60 ml/min/1.73m^2) in the fifth year after transplantation. Doses of cyclosporine and the serum level of cyclosporine did not differ in patients who had a decreased GFR from those whose renal function remained normal, which suggests that nephrotoxicity is the result of individual susceptibility to cyclosporine; the same situation has been suggested by Waser et al (11). Tacrolimus also causes vasocon-

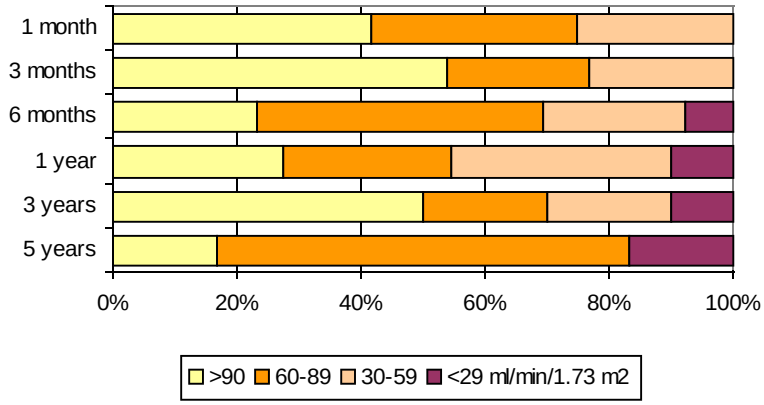

Figure 1a. Evolution of eGFR in patients immunosuppressed with cyclosporine, five years after transplantation

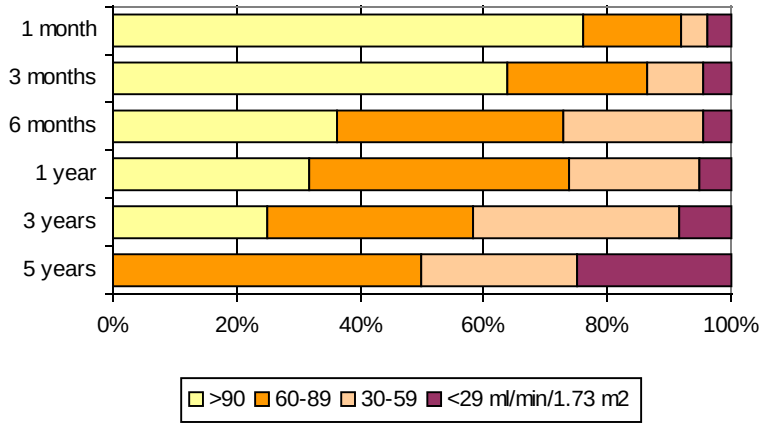

Figure 1b. Evolution of eGFR in patients immunosuppressed with tacrolimus, five years after transplantation

striction in the renal vascular bed and, in chronic administration, it causes pathological changes such as nodular arteriolar hyalinosis, arteriolar intimal necrosis, fibrosis, tubular and interstitial atrophy (2). In our group treatment with tacrolimus was initiated in 23 patients of whom 19 survived one year; in two of them significant decrease in glomerular filtration rate occurred already at one year after transplantation (from 110 ml/min/1.73m^2 to 37 ml/min/1.73m^2, respectively from 83.4 ml/min/ 1.73m^2 to 49.5 ml/min/1.73m^2).

Evolution of the eGFR depending on specific immunosuppressive therapy is shown in *Figure 2*.

The changes in eGFR according to the immunosuppressive medication showed a significant reduction of eGFR in medium-term (three years) daily administration of tacrolimus (73.1 ± 41.81 to 52.4 ± 12.1 ml/min/1.73m^2, p=0.0177) or cyclosporine (98.8 ± 62.38 to 65.2 ± 32.57 ml/min/1.73m^2, p=0.0140). Overall, significant chronic decrease in kidney function occurred in 25% of our patients treated with tacrolimus and in 20% of the patients treated with cyclosporine. The results of studies comparing the incidence of chronic kidney disease among non-renal transplant recipients receiving calcineurin inhibitors - based immunosuppressive regimens vary widely

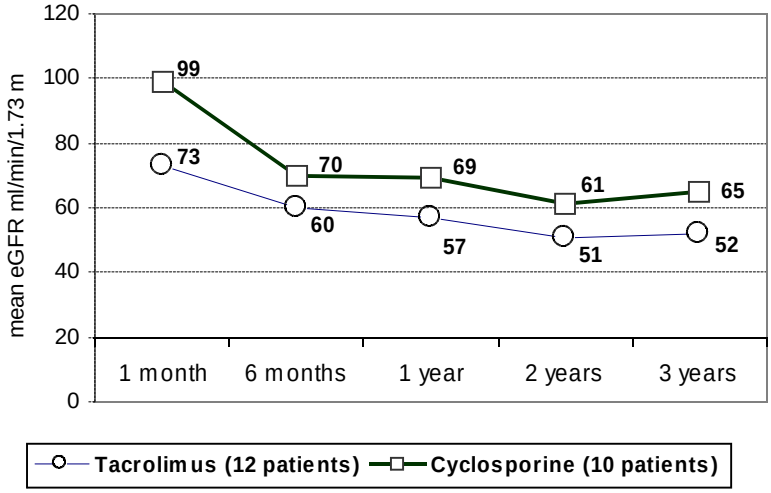

Figure 2. Evolution of mean eGFR according to immunosuppressive treatment, from 1 month to 3 years post-transplantation

from 4 to 85% (7, 12, 13). In our study the risk of chronic renal failure increased over time, ranged from 5% at first months after transplant to 50% at the end of fifth year. In studies comparing the risk of chronic kidney failure among non-renal transplant recipients receiving cyclosporine-based immunosuppressive treatments with recipients receiving tacrolimus-based regimens, the results have been contradictory (14-16). The risk of chronic renal failure is higher among liver-transplant recipients receiving cyclosporine- than among tacrolimus-based immunosuppressive regimens - a difference that was not obvious in patients with other types of solid-organ transplants (2, 7). The mortality rate in our group was 17.1% (27.3% in patients with cyclosporine and 12.5% in patients with tacrolimus), comparing to 8-20% in other studies (7, 13), but only one patient from six died because of renal failure.

The importance of patient age at the moment of transplantation

We analyzed the evolution of glomerular filtration rate according to the age at which heart transplantation was performed. Distribution of recipients by decade of age at the time of transplantation was balanced (*Table 3*).

A marked decrease in eGFR after transplantation is associated with older age of patients undergoing transplantation. The older the patient's age, the faster and more marked is the GFR decrease. Similar results are mentioned by other studies (17, 18). According to Przybylowski et al (19) serum neutrophil gelatinase-associated lipocalin (NGAL) could be a more sensitive marker of kidney function than eGFR, in patients older than 65 years of age.

The importance of gender in the development of renal dysfunction after cardiac transplantation

Our study included a total of 26 men (74.28%) and 9 women (25.72%). The mean age was 40 years for men and 30 years for women. The mean eGFR were lower in men than in women at each of the analyzed stage post-transplant, but differences are not statistically significant. Values calculated during global tracking and rendered are displayed in *Figure 3*. According to data from previous studies, female gender was identified as predictor for an increased risk of chronic renal disease (17, 18). The difference in mean age and small number of patients did not permit us to obtain a pertinent conclusion on this variable.

Table 3. Distribution of recipients by age (at the time of transplantation) and eGFR at one month, one and three years

Age (Years)	1 month		1 year		3 years	
	no.	Mean±SD*	no.	Mean±SD*	no.	Mean±SD*
< 20	6	149.9±38.3	6	99.6±28.4	3	107.5±6.14
21-30	7	175.9±42.6	7	117.7±32.3	4	116.2±33.87
31-40	7	95.6±48.8	7	69.3±23.9	6	62.6±27.38
41-50	6	80.6±40.2	5	69.7±36.12	4	53.4±29.07
>50	9	90.1±24.4	7	56.3±18.8	5	45.85±17.19

*mean eGFR

Hypertension and diabetes

An important role in renal dysfunction is the presence of hypertension and diabetes. We obtained a clear difference between eGFR in patients suffering from hypertension and those who do not develop the disease: at six months after transplantation, patients with hypertension (9/35) had significantly lower eGFR comparative with normotensive patients (64.9±28.7 ml/min/1.73m^2 vs 90.2±29.2 ml/min/1.73m^2, p=0.01). Current guidelines recommend strict control of blood pressure (20, 21), some small studies supporting the nephroprotective effect of calcium channel blockers in heart transplanted patients treated with calcineurin inhibitors.

At six months 9 in 35 patients and at one year 7 in 32 patients had diabetes. At six months eGFR in patients without diabetes was slightly higher thand in patients with diabetes (82±33 vs 74.3±26.5 ml/min/1.73m^2, p=0.32), but two diabetic patients had an eGFR decrease below 60ml/min. Diabetes does not cause changes in kidney function at six months after transplantation, but after one year the average eGFR in diabetic patients is significantly lower (62.1±35.9 vs 88.6±33.4 ml/min/1.73m^2, p=0.05). Diabetes also causes faster progression of renal microvascular injury. In diabetic patients the eGFR decline under 60ml/min/1.73m^2 is faster and more important than in patients without diabetes. At one year we monitored 32 patients of which 7

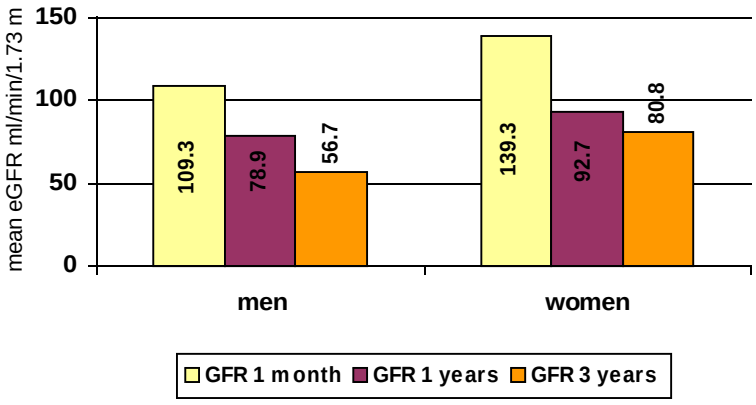

Figure 3. Evolution of mean eGFR from 1 month to 3 years post-transplantation according to gender

had diabetes, four of them showing a GFR below 60 ml/min/1.73m^2.

It is possible that all these factors are adding up their action on the renal function, their combination increasing the risk of renal failure in cardiac transplant patients.

An important limitation of our study emerged from small number of patients: at this moment we did not analyze cardiovascular risk factors like dyslipidemia and insulin resistance, which are recognized side effects of immunosuppressive regimens and contributors to chronic kidney disease.

Conclusions

We observed a significant decrease of renal function in heart transplant recipients on calcineurin inhibitors based immunosuppressive regimens. There is a more marked initial decrease in the early post-transplant period (six months), followed by a slower decline of renal function, late post-transplant. Older age at the time of transplant, time since the transplant, hypertension and diabetes mellitus increase the risk of renal failure in cardiac transplant recipients.

References

1. Calne RY, Rolles K, White DJ, Thiru S, Evans DB, McMaster P, et al.- Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet, 1979 Nov 17; 2(8151):1033–6.
2. Fung JJ, Eliasziw M, Todo S, Jain A, Demetris AJ, McMichael JP, et al. The Pittsburgh randomized trial of tacrolimus compared to cyclosporine for hepatic transplantation. J Am Coll Surg, 1996; 183:117-25.
3. Hopkins PMA - Pharmacological Manipulation of the Rejection Response, in Hornick P, Rose M eds. -Transplantation Immunology-Methods and protocols, Humana Press, 2006, p. 375-400
4. Bennett WM, DeMattos A, Meyer MM, Andoh T, Barry JM – Chronic cyclosporine nephropathy: the Achille's heel of immunosuppressive therapy. Kidney Int, 1996; 50: 1089-100.
5. Greenberg A, Thompson ME, Griffith BJ, Hardesty RL, Kormos RL, El-Shahawy MA, et al. - Cyclosporine nephrotoxicity in cardiac allograft patients: A seven year follow up. Transplantation, 1990, 50: 589-93.
6. Greenberg A, Egel JW, Thompson ME, Hardesty RL, Griffith BP, Bahnson HT, et al. - Early and late forms of cyclosporine nephrotoxicity: Studies in cardiac transplant recipients. Am J Kidney Dis, 1987, 9:12-22.
7. Ojo AO, Held, PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al- Chronic Renal Failure after Transplantation of a Nonrenal Organ, N Engl J Med, 2003, 349 (10): 931-40.
8. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. - Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med, 2006, 145(4):247–54.
9. Miller WG - Glomerular Filtration Rate. The Importance of Standardized Serum Creatinine in Detecting Kidney Disease, Clinical Laboratory News, 2011, 37 (12), p.10-2.
10. Myers BD, Sibley R, Newton L, Tomlanovich SJ, Boshkos C, Stinson E, et al. - The long-term course of cyclosporine-associated chronic nephropathy. Kidney Int, 1988, 33: 590-600.
11. Waser M, Maggiorini M, Binswanger U, Keusch G, Carrel T, von Segesser L, et al. - Irreversibility of cyclosporine-induced renal function impairment in heart transplant recipients. J Heart Lung Transplant, 1993, 12:846 -50.
12. Norman SP, Ojo AO – Chronic Renal Failure after Transplantation of a Nonrenal Organ, Trends Transplant, 2009, 3 (2): 59-69.
13. Al Aly Z, Abbas S, Moore E, Diallo O, Hauptman PJ, Bastani B -The natural history of renal function following orthotopic heart transplant, Clin Transplant, 2005;19(5):683-9.
14. Waller JR, Murphy GJ, Metcalfe MS, Sandford RM, Pattenden CJ, Nicholson ML. Primary immunosuppression with tacrolimus is associated with a reduction in renal allograft fibrosis compared with neoral therapy. Transplant Proc, 2002;34:1587-8.
15. English RF, Pophal SA, Bacanu SA, et al. Long-term comparison of tacrolimus- and cyclosporine-induced nephrotoxicity in pediatric heart-transplant recipients. Am J Transplant, 2002;2:769-73.
16. Flechner SM, Kobashigawa J, Klintmalm G - Calcineurin inhibitor-sparing regimens in solid organ transplantation: focus on improving renal function and nephrotoxicity, Clinic Transplant, 2008, 22(1): 1-15.
17. Hamour IM , Omar F, Lyster H S, Palmer A and Banner NR - Chronic kidney disease after heart transplantation, Nephrol Dial Transplant, (2009) 24: 1655–1662.
18. Corman SL, Coley KC and Schonder KS - Effect of Long-term Tacrolimus Immunosuppression on Renal Function in Liver Transplant Recipients, Pharmacotherapy, 2006, 26, p. 1433-7.
19. Przybylowski P, Malyszko J, Malyszko J. - Kidney

function assessed by eGFR, cystatin C and NGAL (neutrophil gelatinase-associated lipocalin) in relation to age in heart allograft recipients, Med Sci Monit, 2010, Sep;16(9):CR440-4.
20. Lindelo BW, Bergh CH, Herlitz H, Waagstein F - Predictors and Evolution of Renal Function during 9 Years Following Heart Transplantation, J Am Soc Nephrol, 2000, 11: 951–957.
21. The international society of heart and lung transplantation guidelines for the care of heart transplant recipients, TASK FORCE 3: Long-term Care of Heart Transplant Recipients, August 6, 2010, http://www.ishlt.org/ContentDocuments/ISHLT_GL_TaskForce3_080610.pdf