CARDIOVASCULAR RISK IN ESRD PATIENTS ON THE TRANSPLANT WAITING LIST FOR RENAL TRANSPLANTATION

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Abstract

Renal transplantation represents the main method of renal substitution in uraemic patients. The decreased supply of organs, in the conditions of a high organ demand, has determined an increasing number of patients on the waitinglist, and also of the cardiovascular events. The purpose of our study is to establish the frequency and the gravity of the cardiovascular events, as well as the associated risk factors existing in uraemic patients that were included or not in renal substitution treatment programs, prior to inclusion on the transplant waitinglist, in the Nephrology Center of the «Fundeni» Clinical Institute. The material used for this study included 432 cases (236 men, 196 women, mean age=47,7years) diagnosed with end stage renal disease (serum creatinine ≥ 6 mg%, Cl Creatinine < 15 mg%), based on the international ERA-EDTA criteria. The patients were divided into three groups: group A contained the non-dialyzed patients (137 cases), group B contained patients undergoing hemodialysis (202 cases) and group C contained patients undergoing peritoneal dialysis (CAPD). The mean follow-up period was 11,9 months (1-119). Patients suffering from severe heart failure ($\geq$ stage IV NYHA), severe respiratory failure, stage Childs C liver cirrhosis, HIV infection, active infectious diseases, advanced neoplasia, age over 70, patients who refused, were not included in this study. 8,3% (36/432) received a transplant, and 8,1% died (35/432). Mortality rate was significantly lower ($p<0.05$) in patients undergoing peritoneal dialysis (2,1%), compared to those non-dialyzed (15,3%) or those undergoing hemodialysis (5,9%). The main death causes were: major heart arrhythmias (34,5%), stroke (20%), sudden death (5,7%), pulmonary embolism and acute pulmonary oedema (2%). The rate of cardiovascular disease was 81,0% for the non-dialyzed patients, 73,8% for patients undergoing hemodialysis and 84,9% for those undergoing peritoneal dialysis. The most frequent clinically identified cardiovascular disease was arterial hypertension, with a significantly higher prevalence ($p<0,05$) in the non-dialyzed uraemic patients (80,3%), compared to the hemodialyzed patients (61,4%) or CAPD patients (64,5%). The prevalence of ischaemic heart disease with ECG modifications was 13,7%, of major arrhythmias was 10,4%, and of heart failure was 9,5%, with a significantly higher frequency among patients undergoing dialysis, probably because of the haemodynamic, atherogenic, electrolyte etc. changes that are induced by hemodialysis, or because patients suffering from cardiovascular illnesses were included in the peritoneal dialysis program (19,2% in hemodialyzed patients and 15,0% in patients undergoing peritoneal dialysis versus 5,6% in those non-dialyzed, $p<0,05$). In conclusion the global mortality rate on the renal transplant waiting list was of 8,1%/year, the mortality causes being mainly of cardiovascular nature: arrhythmias and stroke. Cardiovascular morbidity was high, over 70% for

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the non-dialyzed, hemodialyzed or CAPD uraemic patients suffering from cardiovascular illnesses. Arterial hypertension, arrhythmias, stroke, heart failure, pulmonary embolism are the main causes of morbidity in the uraemic patients on the renal transplant waiting list, whether or not they are included in a dialysis programme. Dialysis does not reduce the risk of cardiovascular events in uraemic patients that are on the renal transplant waiting list, on the contrary, the rate of cardiovascular morbidity and mortality are significantly higher in these cases.

Key words: peritoneal dialysis, renal transplantation, cardiovascular risk, ESRD patients

Introduction

Renal transplantation represents the main therapeutic method of renal substitution in uraemic patients. European Best Practice Guidelines for Renal Transplantation recommends that all uraemic patients must be considered for renal transplantation, except those that have absolute contraindications: advanced and therapeutically exceeded neoplasia, active systemic infections, diseases with a survival rate under 2 years (1). Although infections, neoplasia, cardiovascular or gastrointestinal illnesses determine high morbidity and mortality post-transplantation (evidence level B), they are not considered contraindications, because the renal transplantation offers a higher life expectancy and a better quality of life than does dialysis (evidence level A), at a significantly lower cost (10.000 vs. 16.000\$/year). The death rate in the first year after transplantation is 5-7%, compared to the 12-27% annual mortality rate in dialyzed patients (2).

In the past years, the renal transplantation has become the victim of its own success. In the conditions of high demand, the organ offer has decreased permanently, so that the waiting list has developed uncontrollably, becoming an unsafe medical space. In the USA, the mortality rate on the waiting list exceeds 25% per year, cardiovascular diseases being the main cause of death (UNOS – United Network for Organ Sharing). Epidemiological studies have shown that 70% of uraemic patients suffer from cardiovascular illnesses, by accumulating classic risk factors with those generated by uraemia and renal substitution procedures (dialysis). In case of uraemia, arterial hypertension and atherosclerosis occur early and evolve quickly, therefore in uraemic patients, the prevalence of hypertension is 5-6 times higher, and that of acute myocardial infarction is 20 times higher than in the witness group. In uraemic patients, the cardiovascular mortality is 10 times higher compared to the

witness population. UNOS states that cardiovascular illnesses provide over 50% of the total deaths in uraemic patients, the main cardiovascular mortality causes being heart failure, acute myocardial infarction, and sudden death.

Detecting uraemic patients with high cardiovascular risk has become a major objective. Our study aims to evaluate the cardiovascular morbidity and mortality particularities and the cardiovascular risks in uraemic patients that are on the renal transplant waiting list in a nephrological university center.

Materials and Methods

In 1996, the Fundeni “Internal Medicine and Nephrology” Center has initiated a prospective study on evaluating the cardiovascular morbidity and mortality in uraemic patients that were on the renal transplant waiting list, and determining the main risk factors and causes of the cardiovascular morbidity and mortality.

The patients

432 patients were included in the study, of which 236 being men and 196 – women, the mean age was $47,7 \pm 17$ (16-70) years, the uraemia diagnosis was based on the ERA EDTA diagnostic criteria: persistent serum creatinine ≥ 6 mg%. To assess the dialysis impact on the cardiovascular risk, the patients were placed in three groups and analyzed separately: group A, with 137 nondialyzed patients, group B with 202 hemodialyzed patients, and group C with 93 CAPD patients. The exclusion criteria is presented in table 1.

Study plan

Patients were monitored through periodical exams performed every 6 months. The main clinical parameters were registered (arterial hypertension, HR, existence of cardiac murmurs), biological

Table 1 - Study inclusion and exclusion criteria

- inclusion criteria:

- serum creatinine ≥ 6 mg%;
- included or not in a dialysis programme (hemodialysis, peritoneal dialysis).

- exclusion criteria:

- age > 70 years
- severe systemic disorders:
  - ◆ severe heart failure NYHA class IV
  - ◆ severe respiratory failure
  - ◆ chronic liver disease Child C stage
  - ◆ decompensated* diabetes mellitus
  - ◆ active tuberculosis*
  - ◆ end stage neoplasia
- patient's refusal

*temporary exclusion criteria

(creatinine, urea, uric acid, cholesterol, lipids, triglycerides, glycaemia, serum ions, complete blood count), cardiologic echography (diameters of heart cavities and aorta, LV posterior wall and iv septum thickness, LV ejection fraction, valvular calcification, existence of fluid in the pericardium), classic ECG (heart rhythm, heart rate, QRS axis, LV hypertrophy, end phase modifications), BP and ECG monitoring. Clinical, biological, and cardiological data were registered in a monitoring matrix, separately for each study group. Endpoints tracked for each group were: global mortality, global cardiovascular morbidity and arterial hypertension, ischaemic cardiopathy with ECG modifications, acute myocardial infarction – lethal and nonlethal, major arrhythmias (paroxysmal supraventricular tachycardia, atrial fibrillation and flutter, ventricular extrasystoles and fibrillation), heart failure and stroke (table 2).

Statistical analysis

Statistical interpretation of the data obtained from the research files has been made by using the statistical program SPSS, version 6.0 for Windows. The frequency of the tracked parameters was determined separately for each of the three patient groups, and the frequencies were compared to each other. The relative risk and the trust interval was 95% were used to estimate the significance of observed differences. The threshold of statistical significance has been established at a value of $p < 0,05$.

Table 2 - Morbidity and mortality causes in uraemic patients

- Atrial hypertension;
- Acute myocardial infarction;
- Angina, major arrhythmias;
- Heart failure;
- Stroke

Results

Demographic characteristics of the patients included in the study

432 patients were included in the study. Demographic, clinical and laboratory data are presented in table 3. Mean follow-up time was 11,9 months (1-119). Data of patients who had died in the first month from inclusion in the study were excluded, since the cause of death in these cases is the advanced kidney disease itself and/or complications linked to late initiation of a dialysis program.

Patients were placed into 3 groups:

- Group A: non-dialyzed uraemic patients $n=137$;
- Group B: hemodialyzed uraemic patients $n=202$;
- Group C: CAPD uraemic patients $n=93$ (fig. 1).

Transplant rate in the enrolled patients

Renal transplantation was performed in 36 out of 432 (8,3%) cases during the whole follow-up period. In 10 out of 36 cases, the transplantation was performed on patients that were not included in a dialysis program, while the rest of 26 cases, the renal transplantation was performed on patients who were included in a dialysis program for a variable amount of time. The kidney graft came from a live donor in 83,3% of the cases (30/36 patients), and from a cadaveric donor in 26,7% of the cases (6/32 patients). (fig. 2)

Table 3 - Demographic data of patients eligible for renal transplantation

Sex (M/F)	236/196
Mean age (years)	47,4 +/- 17,0 (17-69)
Serum creatinine at inclusion (mg/dl)	9,9 +/- 3,3
Follow time (months)	11,6 +/- 17,9 (1-119)

Figure 1 - Repartition of uraemic patients included in the study

Figure 2 - The rate of renal transplantation in the studied group

The morbidity rate and causes in uraemic patients on the renal transplant waiting list

111/1372 (81,0%) of the uraemic patients presented comorbidities associated to the chronic kidney disease. (fig. 3)

Statistical analysis of the morbidity causes in uraemic patients showed that arterial hypertension represents the main morbidity cause in this patient category, 80,3% of the uraemic patients having high blood pressure. (table 4)

Morbidity rate and causes in uraemic patients on the renal transplant waiting list, undergoing hemodialysis (table 5)

Morbidity rate and causes in uraemic patients on the renal transplant waiting list, undergoing CAPD

In this patient category, the morbidity rate was 84,9% (79/93), the main cause of morbidity being HBP, 64,5% of the patients suffering from it. (table 6)

There are no statistically significant differences between global morbidity rates of all the three groups: 81,0% in nondialyzed patients, 73,8% in HD patients, and 84,9% in CAPD patients.

Cardiovascular morbidity in uraemic patients on the renal transplant waiting list

The main cause of cardiovascular morbidity in uraemic patients on the renal transplant waiting list was arterial hypertension, with a frequency rate significantly higher in predialysis uraemic patients, compared to those already included in hemodialysis or CAPD programs (80,3% vs. 61,4% in HD and 64,5% in DPCA; $p < 0,05$). Existence rate for HBP in patients undergoing HD isn't different than that in the DPCA patients ($p > 0,05$). Other cardiovascular morbidity causes were represented by: angina,

Figure 3 - Global comorbidity rate in uraemic patients

Table 4 - Morbidity causes in predialysis for uraemic patients

HBP n=110 (80,3%)
Infection n=11 (8,0%)
Stroke n=1 (0,7%)
AMI n=1 (0,7%)
Angina n=2 (1,4%)
Major arrhythmias n=2 (1,4%)
Heart failure n=2 (1,4%)
Tuberculosis n=1 (0,7%)
Cancer n=1 (0,2%)
Chronic liver dysfunctions n=6 (4,6%)

Table 5 - Morbidity causes in uraemic patients on the waiting transplant list, undergoing HD

HBP n=124 (61,4%)
Infection n=43 (21,3%)
Stroke n=5 (2,5%)
AMI n=0
Angina n=12 (5,9%)
Arrhythmias n=12 (5,9%)
Heart failure n=10 (4,9%)
Chronic liver disease n=22 (10,9%)
Tuberculosis n=2 (0,9%)
Cancer n=2 (0,9%)

Table 6 - Morbidity causes in uraemic patients on the waiting transplant list, undergoing CAPD

HBP n=60 (64,5%)
Infection n=31 (33,3%)
Stroke n=1 (1,1%)
AMI n=1 (1,1%)
Angina n=6 (6,4%)
Arrhythmias n=3 (3,2%)
Heart failure n=3 (3,2%)
Chronic liver disease n=19 (20,4%)
Tuberculosis n=2 (2,1%)
Cancer n=3 (3,2%)

arrhythmias, and heart failure in dialyzed patients, because of the hemodynamic modifications induced by the fistula or the choice of CAPD for uraemic patients with cardiac illnesses, or because of the hydro-electrolytic dysfunction induced by dialysis (19,2% in HD and 15% in CAPD vs. 5,6% in non-dialyzed patients, $p < 0,05$).

The most frequent non-cardiovascular morbidity causes were infections, more common in dialyzed patients compared to those non-dialyzed, due to the presence of the catheter (8,0% vs 21,3% in HD and 33,3% in CAPD, $p < 0,05$) and chronic liver diseases, also more common in dialyzed patients, due to nosocomial contamination during HD and preferential allotment of infected patients in the CAPD program (4,6% in non-dialyzed uraemic patients vs. 10,9% in HD and 20,4% in CAPD). (table 7).

Rate and mortality causes in uraemic patients on the renal transplant waiting list

35 (8,1%) of the patients died, the most frequent causes being cardiovascular events (arrhythmias, stroke, sudden death) and infections. The global mortality rate was 8,1%/year. (table 8)

Cardiovascular mortality in uraemic patients on the renal transplant waiting list.

In 65,7% (23/35) of the cases, death was due to cardiovascular causes. Cardiac arrhythmias, most frequently caused by hydro-electrolyte disorders, represented the cause of death in 34,3% of the total deaths. Other cardiovascular death causes in patients on the renal transplant waiting list were stroke, sudden death, pulmonary aedema and pulmonary embolism. (table 9)

The rate of cardiovascular mortality was 5,3%/year. Compared statistical analysis showed a significantly higher frequency of cardiovascular

Table 7 - Cardiovascular morbidity in uraemic patients on the renal transplant waiting list

Parameter	Non-dialyzed patients	HD	CAPD
Hypertension*	80,3%*	61,4%	64,5%
Cardiovascular disease**	5,6%**	19,2%	15,0%
Infections	8,0%	21,3%	33,3%
Chronic liver disease	4,6%	10,9%	20,4%

* $p < 0,05$; Non-dialyzed vs HD, CAPD

** $p < 0,05$; cardiovascular morbidity vs. other morbidity cause

Table 8 - Causes of death in uraemic patients on the renal transplant waiting list

Arrhythmias n=12 (34,3%)
Stroke n=7 (20%)
Cardiac arrest n=2 (5,7%)
Pulmonary aedema n=1 (2,8%)
Pulmonary embolism n=1 (2,8%)
Sepsis n=7 (20%)
Pulmonary infections n=1 (2,8%)
Cancer n=1 (2,8%)
Total n=35 (8,1%)

Table 9 - Cardiovascular mortality in uraemic patients on the renal transplant waiting list

Arrhythmias n=12 (34,3%)
Stroke n=7 (20%)
Cardiac arrest n=2 (5,7%)
Pulmonary aedema n=1 (2,8%)
Pulmonary embolism n=1 (2,8%)
Total n=23 (5,3%)

mortality, comparing to other causes of death ($p > 0,05$). 91,3% of the patients who died from a cardiovascular cause, suffered from HBP. Depending on the presence or absence in a dialysis program, global and cardiovascular mortality were lower in the CAPD patients, in comparison with the non-dialyzed uraemic patients or those undergoing hemodialysis ($p < 0,05$)(table 10). None of the CAPD patients died by a cardiovascular cause. (table 11)

Discussion

Numerous epidemiological studies have confirmed the better survival rate in patients with renal transplantation compared to those who are

Table 10 - Mortality rate in uraemic patients on the renal transplant waiting list

Global mortality	Non-dialyzed patients	HD	CAPD
35 (8,1%)	21 (15,3%)	12(5,9%)	2 (2,1%)*
Cardiovascular mortality/ Global mortality	CKD end stage	HD	DPCA
21 (65,7%)	15 (71,4%)	6 (50%)	0

*p<0,05; CAPD vs HD, non-dialyzed patients

Table 11 - Death causes in uraemic patients on the renal transplant waiting list

	Total	End-stage CKD	HD	CAPD
Stroke	7	6	1	0
Arrhythmias	12	9	3	0
Sudden death	2	0	2	0
Sepsis	7	2	4	1
Other infections	2	1	1	0
Other	5	3	1	1

dialyzed: the 5 year survival rate is 94% for renal transplantation from a live donor, 76% for renal transplantation from a cadaveric donor and 60% for dialyzed patients. The data gathered from a comparative study on mortality in dialyzed patients compared to mortality in dialyzed patients on the renal transplant waiting list and in transplanted patients, has shown that the mortality rate is lower in patients on the renal transplant waiting list (6,3%/year), compared to dialyzed patients who weren't on the waiting list (16,1%/year). The relative risk of death is significantly lower in transplanted patients, compared to the patients on the renal transplant waiting list (2,8 times in 2 weeks post-transplantation) (4). Other studies have shown that there aren't any significant differences between the global mortality in the two categories of patients. Nevertheless, a recent study conducted by UNOS, showed that mortality was higher in patients with a longer period of waiting on the transplant list. The lack of consistency could be due to comparing studies held in different eras and different periods of time before the renal transplantation was performed. Mortality and morbidity are high in the first 6 months post-transplantation and they subsequently decrease to values lower compared to those in patients that are undergoing dialysis (5).

The results of this study and other studies published in medical literature draw attention on the presence of HBP and other cardiovascular diseases in patients included in dialysis programs.

Therefore, in a study on a population of 2535 adult dialyzed patients, the HBP prevalence was 86% (6,7). The high prevalence of ischemic heart disease was also observed, considering that 34% of patients with CKD had a history of cardiovascular disease, and 21% of them have been diagnosed through echocardiography with LV hypertrophy. HBP was also reported in uraemic patients, with a prevalence of 60-76% (8, 9, 10). According to NKF – DOQI (National Kidney Foundation – Dialysis Outcomes Quality Initiative) the presence of cardiovascular disease is the defined in non-dialyzed uraemic patients by the existence of congestive heart failure or ischemic heart disease or LV hypertrophy, and has a global prevalence of 8-40%. At least 35% of the uraemic patients have an ischaemic episode (acute myocardial infarction or angina) when initiating dialysis (11). The prevalence of arterial hypertension, as a risk factor for ischaemic heart disease or LV hypertrophy, is extremely high in this patient category: 87-90%.

In our study, the HBP prevalence in non-dialyzed patients is 80,3%, similar to literature data. It has been observed a statistically significant prevalence reduction of HBP through fluid control, in patients included in a dialysis program (61,4% in HD and 64,5% in CAPD vs. 80,3% in non-dialyzed patients, p<0,05). Hypertension and other cardiovascular events (arrhythmias, stroke, heart failure) are the main morbidity causes in uraemic patients on the renal transplant waiting list, included or not in a dialysis program. Global and cardiovascular

mortality were lower in patients undergoing CAPD, in comparison with non-dialyzed uraemic patients, and HD patients (2,1%/year vs. 15,3%/year in non-dialyzed patients and 5,9%/year in patients included in HD; $p < 0,05$). None of the patients undergoing CAPD did not die by cardiovascular causes, since they received preferential selection and care, as well as due to the absence of haemodynamic stress induced by hemodialysis.

In 2001, in the USA, UNOS reported 50.000 uraemic patients on the waiting list, out of which only 9000 receive annually a renal graft, therefore in 2010 the waiting list included 100.000-150.000 people and the waiting period extended to 10 years. Monitoring these patients was important, given that the annual death rates on the UNOS waiting list is 25%, the cardiovascular diseases representing the main cause of death. In our study, death rates were lower (8,1%) thanks to strict patient monitoring and cardiovascular risk factors power control. Literature data attest that, in the USA, only 8% of the transplant programs perform a thorough cardiac screening on patients that are on the transplant waiting list, 19% perform the screening on diabetic patients, 53% perform the screening on patients with a history of coronary disease, 18% of the programs do not perform any cardiac screening. Control frequency was fluctuating. In 79% of the programs, cardiac monitoring was performed annually. Cardiac monitoring methods were different, including myocardial perfusion scintigraphy, dobutamine echocardiography, coronarian angiography etc (12). In our study, investigation plans were limited, relying on clinical and biochemical investigation, BP and ECG monitoring, and bi-plan and Doppler echography. The myocardial perfusion scintigraphy and angiography were used only to confirm acute myocardial infarction or coronary disease. We consider our results encouraging and they form an algorithm of cardiovascular screening of the patients on the renal transplant waiting list.

Conclusions

Renal transplantation is the election method in treating uraemic patients. The method is limited by the decreased organ supply, the rate of renal transplantation in our study being 8,3%. The rate of global mortality was 8,1%, and the cardiovascular

mortality rate was 5,3%. The main causes of cardiovascular mortality were arrhythmias and stroke. The cardiovascular event rate reached 81,0% in non-dialyzed patients, 84,9% in CAPD patients, and 73,8% in patients undergoing hemodialysis. Cardiovascular morbidity was highly elevated in uraemic patients, who were included, or not in a dialysis program.

Thorough cardiovascular screening of the patients who were on the transplant waiting list was possible and necessary. Bi-annual cardiac screening is mandatory in all patients on the waiting list, not only in patients with high cardiovascular risk, like diabetics or those with a history of coronary disease.

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