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Title: Factors Affecting Adverse Effects after Renal Transplantation

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Abstract

Objective: The incidence of developed adverse effects in the recipients after renal transplantation were analyzed.

Methods: A total of 206 patients (mean age was 41.40±11.88 years, 92.7% were between 46 to 59 years old, and 66.0% were male) who underwent renal transplantation between 2011 to 2016 years were evaluated retrospectively. Information regarding the sociodemographic characteristics of the sample patients were collected with the "Sociodemographic Characteristics Data Collection Form", which was created by the researcher.

Results: Various advers effects were detected in 206 patients who participated in our study. The incidence of advers effects was significantly higher in the patients who had hypertension and chronic glomerulonephritis who underwent dialysis treatment during 0-12 months before renal transplantation, and who received a kidney transplant from a living donor (p=0.001).

The incidence of advers effects related to the immunosuppressive drugs used aftertransplantation was significantly higher in the patients receiving mycophenolate mofetil+ steroid + tacrolimus and mycophenolate mofetil+steroid + cyclosporin, and weight gain was higher in the patients receiving the same group of drugs (p=0.001).

There were no significant differences in terms of advers effects that occurred in other drug combinations

Conclusion: We found that many factors (immunosuppressive drugs, etc.) in patients with renal transplantation may be associated with the incidence of advers effects.

Keywords: Kidney transplantation, Immunosuppressive therapy, Calcineurin inhibitors, Side effects, Dialysis

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Introduction

Chronic Renal Failure (CRF) is an important public health problem in our country and the world due to its increased incidence and high treatment cost. Diabetes, hypertension and glomerular diseases play an important role in the etiology of CRF. The most common causes of CRF in world are these three chronic diseases (1). The options for Renal Replacement Therapy (RRT) in patients diagnosed with End-Stage Renal Disease (ESRD) are dialysis (hemodialysis orperitoneal dialysis) and kidney transplantation (Tx) (2, 3). RRT is a treatment that imposes a heavy burden on society and not only affects patients but also families due to its high treatment cost. In the United States in 2003, 360,000 people with ESRD were on RRT (4).Tx has been the most successful and most preferred method for patients with CRF thanks to the newly developed surgical methods and the introduction of immunosuppressive drugs (5). However, Tx has some disadvantages besides its advantages. Immunosuppressive drugs that are used to prevent rejection especially in patients who undergo renal transplantation cause advers effects (6). Giving adequate immunosuppressive therapy and providing immunity to protect infections that may occur in the recipient are proportional to the success of renal transplantation and the survival rate of grafts (7). The immune system of the recipient after kidney transplantation should be suppressed by immunosuppressive drugs.

Sufficient immunosuppressive therapy is selected as a combination and is administered to patients (8). The age and gender of the patient, HLA compliance between recipient and donor, and the protocols of transplant centers are taken into account, and immunosuppressive therapy is then selected (9). The main goal in immunosuppressive therapy is to prevent the occurrence of rejection episodes (antigen recognition-costimulation proliferation) by creating a specific pharmacological tolerance against the graft with minimal advers effects (10).

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The selective properties of currently used immunosuppressive therapies are increasing. The combined use of different groups of medicines both provides a synergistic effect and avoids unwanted advers effects by enabling dose reduction. Thus, it is possible to improve the optimal graft survival and the quality of life for transplant recipient (11).

Recently, classical triple immunosuppressive regimen started after Tx consists of Mycophenolate Mofetil (MMF), calcineurin inhibitors and steroid hormone. Mycophenolate mofetil has been used since 1995 and is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenase (IMPDH) (12).

The most common advers effects of MMF use are leukopenia, diarrhea, and gastrointestinal irritation. When used at higher doses, there has been an increase in invasive cytomegalovirus (CMV) disease (13). Calcineurin inhibitors such as tacrolimus and cyclosporine are important immunosuppressive drugs used after Tx and have been found to cause advers effects such as hypertension and diabetes (14). Sirolimus, which is another immunosuppressive drug used after Tx, is an antibiotic with immunosuppressive properties. Sirolimus inhibits the development of T cells and provides a powerful control mechanism on these cells when used with cyclosporine (15). However,this drug has dose-dependent advers effects (hyperlipidemia, diabetes, anemia, thrombocytopenia, proteinuria, edema, impaired wound healing, and mouth ulcers) (16). Corticosteroids (prednisolon, etc.) are drugs that have been used for many years in order to prevent rejection (17). Immediately after starting immunosuppressive drugs in all transplant patients, blood drug levels should be monitored closely. Many studies have proved that nephrotoxicity and kidney failure rates are high when drug levels are not adjusted well (18).In the light of these data, we tried to determine the rates of advers effects in 206 transplant patients and the role of immunosuppressive drugs in these advers effects.

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Materials And Methods

A total of 206 patients (mean age was 41.40±11.88 years, 92.7% were between 46 to 59 years old, and 66.0% were male) who underwent renal transplantation between 2011 to 2016 years were evaluated retrospectively. The inclusion criteria for our study were as follows: being a volunteer, receiving a kidney transplant from either a living or a deceased donor, being over 18 years old, receiving immunosuppressive drugs, having no a mental health illness, lack of inappropriate self- expression, and having completed at least the second month after Tx. A total of 206 patients who met these characteristics were included in the study. Patients were informed about the study by the researcher. Verbal and written informed consent were obtained. The data of the study were collected by the Face-to- Face Interview Technique. The data collection period lasted 15-20 minutes for each individual.

The questions in the questionnaire were read out loudly and clearly by the researcher, and the answers given by the patient were marked on the forms by the researcher. The "Sociodemographic Characteristics Data Collection Form" was prepared by the researcher in order to obtain information about the characteristics of the sample patients. This form included the demographic variables such as age, gender, marital status, education level, family type, occupation, whether or not the patient has been informed about the use of immunosuppressive drugs related to the organ transplantation process by the health personnel, employment status after transplantation, working status, income level and the variables related to the disease such as the cause of kidney failure, how many years the patient has had chronic kidney failure, whether or not the patient underwent dialysis treatment, what type of dialysis treatment the patient received, date of transplantation, donor type, whether or not the patient knew the discomforts that may occur after transplantation, immunosuppressive drugs the patient received, whether or not advers effects occurred, what the patient did when advers effects occurred, whether or not the patient had rejection, and the priority ranking of drugs in the patient's life. Ethics committee approval was obtained before the

study.

Statistical Analysis

Statistical analysis of the data was performed using the IBM SPSS Statics version 23.0 software package (IBM SPSS, Inc., the USA). The 95% Confidence Interval was used. A p-value of <0.05 was considered statistically significant.

Limitations and Generalizability of the Study

The most important limitation of the study is that it was conducted at a single center. Since the study was conducted at an organ transplant center located within a private hospital, low- income patients who need to pay extra money could not refer to this center. Therefore, this study can not be generalized to all transplant patients in Turkey.

Results

The mean age of the patients who participated in our study was 41.40 ± 11.88 years. The age of the patients varied between 18-71 years. 92.7% of the study population consisted of patients aged 46-59 years. When the distribution of the patients according to their genders was examined, 66.0% were male. It was found that 79.1% of the patients were married, 45.2% were literate or primary school graduates, 68.4% were core family members and 26.7% were retired. It was determined that 53.5% of the patients did not continue to work after transplantation and 70.7% of them did not continue to work because they were

retired. It was found that 48.5% of the patients had a balance between their income and expenses. Table-1 shows the distribution of patients according to their sociodemographic characteristics.

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99% of the patients who participated in our study were informed by the health personnel. %92.2 deemed that this informing was sufficient. 35.9% did not know the cause of Chronic Kidney Failure. 30.6% argued that the cause of Chronic Kidney Failure was hypertension. The duration of Chronic Renal Failure in 39.3% of the patients was 121 months and over. It was determined that 88.3% of the transplant patients underwent dialysis treatment, and 29.1% of them had been treated for at least 10 years. Of the patients undergoing dialysis treatment, 85.7% underwent hemodialysis treatment. 52.4% of the patients were between the range of "12-60 months" after transplantation. 54.4% received a kidney transplant from a living donor.

61.2% knew discomforts that can develop after organ transplantation. Table-2 shows the distribution of the patients according to the characteristics of their disease.

93.1% of the patients received MMF+steroid + tacrolimus as immunosuppressive drug after transplantation. Moreover, 18% received antiviral agents, 18.4% received antifungal agents, 55.3% received antihypertensive drugs and 14.1% received antidiabetic drugs. 54.9% of the patients developed advers effects. 72% of those experiencing advers effects gave their doctor information. 2.9% developed rejection due to incompatibility. 94.6% reported that drugs ranked first in their life. Table-3 shows the distribution of the properties of immunosuppressive drugs used after transplantation.

Various advers effects were detected in 206 patients who participated in our study. These advers effects were weight gain (20.08%), acne (4.9%), tremor (4.4%), diabetes (4.4%), hair loss (2.4%), fatigue (1.9%),

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itching (1.5%), irritability (1%), palpitation (1%), stomach pain (1%), osteoporosis (1%), eye complaints (1%), shingles (1%), nausea-vomiting (1%), hairing (0.5%), headache (0.5%), nail fungus (0.5%), lung infection (0.5%), insomnia (0.5%), drowsiness (0.5%), urinary infection (0.5%), weight loss (0.5%), ecchymosis in the skin (0.5%), blockage of the brain vessels (0.5%), tinnitus and numbness in the ear (0.5%), and redness in the body (0.5%), respectively. Table-4 shows the distribution of advers effects after Tx according to their incidence. The incidence of advers effects after Tx was significantly higher in the patients who had hypertension and chronic glomerulonephritis (p=0.001).

When the incidence of advers effects after Tx was compared with the dialysis duration before Tx, the incidence of advers effects (especially weight gain) was significantly higher in the patients who underwent dialysis treatment for 0-12 months (p=0.001).

The incidence of advers effects (especially weight gain) after Tx was significantly higher in the patients who underwent dialysis treatment for 0-12 months (p=0.001).

The incidence of advers effects after Tx was significantly higher in the patients who received a kidney transplant from a living donor compared to the patients who received a kidney transplant from a deceased donor (p=0.001). The incidence of advers effects related to the immunosuppressive drugs used after Tx was significantly higher in the patients receiving MMF+steroid + tacrolimus and MMF+steroid + cyclosporin, and weight gain was higher in the patients receiving the same group of drugs (p=0.001, p=0.001). There were no significant differences in terms of advers effects that occurred in other drug combinations.

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Discussion

It was seen that several advers effects occurred after Tx in the patients included in the study and that these advers effects were mostly compatible with previous studies (19). In our study, when the incidence of advers effects after Tx and the causes of CRF were examined, there was a significant relationship especially in the patients with hypertension and chronic glomerulonephritis (p=0.001). This can be attributed to the larger number of patients with hypertension and chronic glomerulonephritis.

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When the incidence of advers effects after Tx was compared with the dialysis duration before Tx, the incidence of advers effects was significantly higher in the patients who underwent dialysis treatment for 0-12 months (p=0.001). One study reported that increased dialysis duration before transplantation in patients undergoing liver transplantation affected long-term outcomes after transplantation negatively, and was an independent risk factor for increased mortality (20). It can be seen that the results of this study are significantly different when compared to our results. This may suggest that advers effects and negative situations that may be seen after different organ transplantations may be different. Diabetes Mellitus (DM), which is present before or develops newly after kidney transplantation, increases the frequency of infection, disrupts graft function and increases the frequency of cardiovascular diseases, which are the most important causes of mortality in transplant patients (21). Preventable risk factors (hepatitis C and obesity, etc.) as well as uncorrectable risk factors (age, family history, etc.) of newly developed DM after transplantation are gaining importance (22). Especially calcineurin inhibitors and corticosteroids from immunosuppressive drugs used after Tx are among factors that facilitate the occurrence of DM after transplantation (23). Close monitoring of patients after Tx, identification of possible risk factors and early detection of glucose intolerance are important for preventing the development of DM and complications. It was found that 9(4.4%) of the 206 patients included in our group developed DM. Since DM is a well-known risk factor, patients with DM especially in close relatives should be determined, these patients should be followed more carefully in terms of the development of DM after transplantation, and treatments should be planned accordingly. In all solitary organ transplantations including renal transplantation, infections are encountered especially during the first three months after Tx in recipients (24). Studies have shown that infections occur especially in the urinary tract, abdominal area, and chest region (25). In our study, nail fungus, lung infection and urinary tract infection were observed in 0.5% of

the 206 patients (Table-4).

In a study of the majority of patients with Tx were found to have no organ transplant rejection (26). In our study, we found that 2.9% of the patients had organ rejection. In this respect, our findings are similar to the literature. Patients with kidney transplantation (Tx) need immunosuppressive treatment throughout their lifetime. Immunosuppressive regimens used currently for this purpose are administered in combination. The majority of the patients with Tx included in our study received a combined therapy of MMF + steroid + tacrolimus. Our findings are similar to the literature (27). This can be attributed to that the combination of MMF+ steroid + tacrolimus is the most effective combination for immunosuppression.

When it was examined what the participants did after the development of advers effects related to drugs, it was found that the vast majority of them called their doctor. When the literature was examined, no data were found about this finding. Although it is known that immunosuppressive drugs have many advers effects, the impacts of immunosuppressive drugs on weight gain is still unclear (28). Some researchers point out that there is no significant difference between them, but there are publications in the literature that report an opposite opinion (29). Many factors such as the presence of weight gain before transplantation, sedentary life and nutritional recovery after transplantation, and immunosuppressive drugs are thought to play a role in the development of obesity (14).

In our study, when the incidence of advers effects related to immunosuppressive drugs was examined, advers effects were significantly higher in the patients receiving a combined therapy of steroid and tacrolimus, and also, weight gain was significantly higher in the same patient group (p=0.001). Immunosuppressive drugs cause many advers effects in the gastrointestinal tract. In one study, approximately 68% of patients with Tx were found to have severe gastrointestinal complaints in the first year (29).

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Advers effects such as nausea, vomiting and diarrhea were frequently observed especially in patients treated with mycophenolate mofetil (13). Studies have shown that calcineurin inhibitors such as tacrolimus and cyclosporine led to gastrointestinal advers effects (14). In our study, a small proportion of patients were observed with Tx had gastrointestinal advers effects such as nausea and vomiting. Patients who have undergone living donor kidney transplantation, we detected that the incidence of side effects was significantly higher than patients who used cadaver donor (p=0.001). However, literature studies, side effects occurring in recipients of cadaver and, consequently, more of the costs of treatment is found to be (30). This result, the cadaver transplantation more effective and us shows that the idea is more suitable in terms of cost.

In conclusion, we found that many factors in patients with renal transplantation may be associated with the incidence of advers effects.

Informed Consent: Informed consent was obtained from patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors

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Table-1. The distribution of patients according to their sociodemographic characteristics

Sociodemographic characteristics		**n**	**%**
*Age (min-max $\bar{x}$±Sd)	18-71 (41.40±11.88 years)		
Gender	Male	136	66.0
	Female	70	34.0
	Total	206	100.0
Marital status	Married	163	79.1
	Single	43	20.9
	Total	206	100.0
Education level	Illiterate	11	5.3
	Literate- Primary school	93	45.2
	Secondary School-High School	82	39.8
	University and above	20	9.7
	Total	206	100.0
Family type	Core Family	141	68.4
	Extended family	65	31.6
	Total	206	100.0
Occupation	Housewife	52	25.2
	Retired	55	26.7
	Self-employment	42	20.4
	Worker-Officer	57	27.7
	Total	206	100.0
Employment status after transplantation	Yes	87	46.5
	No	100	53.5
	Total	187	100.0

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Reason for leaving work	Changing work	2	2.5
	Leave work	22	26.8
	Being retired	58	70.7
	Total	82	100.0
Income level	High	8	3.9
	Balanced	100	48.5
	Low	98	47.6
	Total	206	100.0

n=number of individuals.
The Student's t-test was used for the analysis of those marked with *.
The data were expressed as mean± standard deviation.

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Table-2. The distribution of the patients according to the characteristics of their disease

Characteristics related to the disease		**n**	**%**
Informing the patients about organ transplantation	Yes	204	99.0
	No	2	1.0
	Total	206	100.0
Informing the patients sufficiently	Yes	190	92.2
	No	16	7.8
	Total	206	100.0
Cause of CRF	Hypertension	63	30.6
	Diabetes	10	4.9
	Chronic glomerulonephritis	25	12.2
	Polycystic kidney disease	4	1.9
	Chronic pyelonephritis	4	1.9
	Infections	19	9.2
	Nephrotic Syndrome	1	0.5
	I do not know	74	35.9
	Hypertension and diabetes	6	2.9
	Total	206	100.0
Duration of CRF	0-12 months	30	14.6
	13-60 months	29	14.1
	61-120 months	66	32.0
	121 months and over	81	39.3
	Total	206	100.0
Dialysis status	Yes	182	88.3
	No	24	11.7
	Total	206	100.0
Duration of dialysis treatment	0-12 months	43	23.6
	13-60 months	39	21.5
	61-120 months	47	25.8
	121 months and over	53	29.1
	Total	182	100.0
Type of dialysis	Hemodialysis	156	85.7
	Peritoneal dialysis	8	4.4

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	Hemodialysis-Peritoneal dialysis	18	9.9
	Total	182	100.0
Time after Tx	2-12 months	57	27.7
	13-60 months	108	52.4
	61-120 months	41	19.9
	Total	206	100.0
Donor type	Living donor	112	54.4
	Cadaveric donor	94	45.6
	Total	206	100.0
Knowing the problems that can develop after Tx	Yes	126	61.2
	No	80	38.8
	Total	206	100.0

n=number of individuals

Table-3: The distribution of the properties of immunosuppressive drugs used after transplantation.

The properties of immunosuppressive drugs		**n**	**%**
Immunosuppressive drugs used after transplantation	MMF+Steroid + tacrolimus	192	93.1
	MMF+Steroid + cyclosporine	8	3.9
	MMF+Steroid + sirolimus	3	1.5
	MMF+Tacrolimus	3	1.5
	Total	206	100.0
Antiviral agents used persistently	Use	37	18.0
	Not use	169	82.0
	Total	206	100.0
Antifungal agents used persistently	Use	38	18.4
	Not use	168	81.6
	Total	206	100.0
Antihypertensive drugs used persistently	Use	114	55.3
	Not use	92	44.7
	Total	206	100.0
Antidiabetic drugs used persistently	Use	29	14.1
	Not use	177	85.9
	Total	206	100.0
Development of advers effects related to drugs	Yes	113	54.9
	No	93	45.1
	Total	206	100.0

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Type of processes performed after the development of advers effects	I stopped using the drug or I reduced its dose	5	5.4
	I called my doctor	67	72.0
	I did not do anything	21	22.6
	Total	93	100.0
Presence of rejection due to incompatibility	Yes	6	2.9
	No	200	97.1
	Total	206	100.0
Priority ranking of drugs in the patient's life	First	195	94.6
	Second	9	4.4
	Third	2	1.0
	Total	206	100.0

n= number of individuals.

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Table-4: The distribution of advers effects after Tx according to their incidence.

Advers effects	**n**	**%**
Weight gain	49	20.8
Acne	10	4.9
Tremor	9	4.4
Diabetes	9	4.4
Hair loss	5	2.4
Fatigue	4	1.9
Itching	3	1.5
Irritability	2	1
Palpitation	2	1
Stomach pain	2	1
Osteoporosis	2	1
Eye complaints	2	1
Shingles	2	1
Nausea-vomiting	2	1
Hairing	1	0.5
Headache	1	0.5
Nail fungus	1	0.5
Lung infection	1	0.5
Insomnia	1	0.5
Drowsiness	1	0.5
Urinary infection	1	0.5
Weight loss	1	0.5
Ecchymosis in the skin	1	0.5
Blockage of the brain vessels	1	0.5
Tinnitus and numbness in the ear	1	0.5
Redness in the body	1	0.5

n= number of individuals.

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