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Original Article

Investigation of Predictive Factors for Function of Transplanted Kidney Graft Based on Zero-Time Biopsy Findings

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HIGHLIGHTS

- The main findings in the zero-time biopsies were acute tubular necrosis, mesangial proliferation, glomerular thrombosis, arteriolar hyalinosis, interstitial fibrosis, and inflammation.
- No significant relationship was found between the zero-time biopsy findings and the graft performance in the short and medium term.
- More glomerulosclerosis and a higher degree of interstitial fibrosis were associated with more DGF.

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ABSTRACT

Introduction
Kidney transplantation is the most definitive treatment for end-stage kidney failure. The purpose of this research is to investigate the impact of zero-time histopathological findings on kidney graft function and survival and the opportunity of performing interferences, based on it, in the immunosuppression regime of transplant patients.

Methods
Patients who underwent kidney transplantation from a deceased donor between 2018 and 2021 in Shariati Hospital were studied. They underwent wedge biopsy of the kidney graft just after reestablishing vascular perfusion, and the samples were subjected to histopathology examination according to the Banff scoring system. Afterward, the patients underwent 1-month, 3-month, and 6-month follow-ups with the serum creatinine levels and estimated glomerular filtration rate.

Results
The main findings in the histopathological examination of the biopsies were acute tubular necrosis (62%), mesangial proliferation (2.5%), glomerular thrombosis (7.2%), arteriolar hyalinosis (7.2%), interstitial fibrosis and inflammation (23%). The score of most of the findings was mild and, C4D was also negative in all patients. Seven patients were affected by the delayed graft function (DGF) and among them, glomerulosclerosis was observed in 57%, arterial intimal fibrosis in 7.1%, and interstitial fibrosis in 8.4%. In the 6-month follow-up, the trend of creatinine and GFR of these patients was not as good as the other patients. Although they were not statistically significant.

Conclusions
Statistically, no significant relationship was found between the zero-time biopsy findings and the graft performance in the short and medium term. Although this is not sufficient for the conclusion due to the small volume of samples.

Keywords: Kidney Transplantation; Zero-Time Biopsy; Deceased Donor; Estimated Glomerular Filtration Rate

Introduction

Kidney failure occurs due to various reasons such as diabetes, hypertension, cardiovascular diseases, and glomerulonephritis. The global burden of this disease is

increasing. This disease and its related treatment measures impose significant economic costs on the healthcare system of countries. When patients reach end-stage renal disease (ESRD), renal replacement therapy (RRT), which includes dialysis or kidney transplantation, is initiated for them. Kidney transplantation is considered the best option for RRT (1).

The goal of kidney transplantation is to free the patient from dialysis and its complications. However, sometimes the transplanted kidney may experience functional disorders, such as acute rejection, and acute or chronic dysfunction. The performance and survival of the transplanted kidney depend on various factors related to the donor, recipient, or the transplantation process (2).

In studies, one of the approaches to investigate these factors, which can predict the performance and survival of the transplanted kidney, is called a zero-time biopsy. The timing of this biopsy varies from before the anastomosis to just after the anastomosis (3).

Underlying conditions such as hypertension, diabetes, and aging lead to pathological changes in the kidney, which significantly affect the survival and function of the transplanted kidney. Zero-time biopsy of the transplanted kidney demonstrates the histopathological characteristics of the donated kidney and these pathological findings can be useful in evaluating the prognosis of the transplanted kidney (1).

This study aims to investigate the function and survival of the transplanted kidney grafts from deceased donors based on the histopathological results of the zero-time biopsy. Additionally, the potential benefits of intervention in the immunosuppressive regimen of patients based on these findings are evaluated.

Methods

This study was conducted as a prospective cohort study between the years 2018 and 2021 at Shariati Hospital, focusing on patients undergoing deceased donor kidney transplantation. All patients entered the study after completing an informed consent form, and this study was registered with the ethics committee under code IR.TUMS.MEDICINE.REC.1398.342.

Patients with ESRD who were undergoing treatment with hemodialysis or peritoneal dialysis and were receiving their first kidney transplant surgery were included in the study. Other inclusion criteria were having a final creatinine level of less than 1.5, ischemia time of fewer than 3 hours, sufficient biopsy sample from the transplanted kidney, presence of a pathology report, and a minimum follow-up period of 6 months. Patients receiving a kidney from a living donor or undergoing a second deceased donor kidney transplantation were excluded from the study. Additionally, patients who experienced graft rejection within one month after surgery or had less than a six-month follow-up period, or had insufficient biopsy samples for pathological examination were also excluded.

Zero-time biopsy samples were obtained using the wedge biopsy technique from the cortex of the graft just after completing the vascular anastomosis, with minimum dimensions of 5×5 millimeters. A single surgeon performed all surgeries and an experienced pathologist according to the Banff scoring system evaluated the samples.

The renal graft function was evaluated by measuring the serum creatinine levels and estimated glomerular filtration rate (eGFR) at 1, 3, and 6 months after transplantation. All demographic and baseline information of the donor (age, gender, cause of brain death, and cardiopulmonary resuscitation) and the recipient (age, gender, type of Renal replacement therapy, cause of ESRD, BMI index, and post-transplant immunosuppressive regimen) were recorded in the designed checklists. Conclusively, the collected data were analyzed statistically using the SPSS software.

Results

Based on the criteria for entering the study, 45 patients were initially included in the study, of which three patients were excluded from the study due to rejection events within one month. Two other patients also refused to continue the follow-up while three patients had suboptimal biopsy samples for examination. Finally, 37 patients were enrolled. No intraoperative or postoperative complications due to the biopsy procedure were encountered.

The most common histopathological findings were acute tubular necrosis (ATN), and mild mesangial proliferation, which are classified as ischemia-related changes in most studies. Other findings were also mild whereas the Glomerular thrombosis was found in one case. C4D was also negative in all patients.

Seven patients were affected by the DGF and among them, glomerulosclerosis was observed in 57%, arterial intimal fibrosis in 7.1%, and interstitial fibrosis in 8.4%. In the 6-month follow-up, the trend of creatinine and GFR of these patients was not as good as the other patients. Although they were not statistically significant.

No significant correlation was found between the serum creatinine level and eGFR with the age and the presence of DM. Although, the recipients with older age and more comorbidities showed slower eGFR increase and the creatinine level decrease.

Conclusively, no statistically significant relationship was found between the histopathological findings and short-term (6 months) graft function (Tables 1, 2).

Discussion

In recent years, various studies have investigated the role of zero-time biopsy or peri-transplantation biopsy in determining the prognosis and survival of the transplanted kidney (4).

Table 1. Correlation between changes in GFR with possible predictive factors

Variables	Categories		β(95%CI)	P-value
Time	Time 0		Ref	
	Time 1		50.69(44053,56.85)	0.00
	Time 3		54.15(47.49,60.30)	0.00
	Time 6		55.72(49.55,61.87)	0.00
Sex	Female		Ref.	
	Male		9.95(-11.83,31.72)	0.370
Age			-.403(-1.20,.39)	0.322
BMI			1.27(-1.006,3.55)	0.274
Comorbidity	Without		Ref.	
	HTN		1.15(-20.36,22.67)	0.91
	DM		7.06(-28.87,43.00)	0.700
	HTN/DM		2.58(-51.91,57.08)	0.92
	HTN/DM/CVA		20.12(-23.8,63.96)	0.36
CPR	No		Ref.	
	Yes		21.32(-10.922,53.56)	0.195
Cause of Brain Death	ACCIDENT		Ref.	
	ALCOHOL		-24.59(-77.53,28.34)	0.36
	BRAIN TUMOR		23.65(-6.33,53.67)	0.12
	FALLING		-8.77(-38.44,20.91)	0.56
	ICH		.44(-27.44,28.34)	0.97
	SIEZURE		-33.94(-86.19,18.30)	0.99
	SUICIDE		.07(-24.48,24.63)	0.99
	TOXICITY		.59(-49.39,50.58)	0.98
Histopathology	Number of glomeruli		.07(-.45,.61)	0.77
	Globally sclerosed glomeruli		8.43(-25.18,42.04)	0.62
	% of global glomerulosclerosis		-1.67(-5.89,2.55)	0.43
	Number of arteries		19.02(-23.41,61.46)	0.38
	Intristial fibrosis	Mild	2.38(-33.23,37.99)	0.89
		Moderate	24.81(-14.58,64.21)	0.27
	Intestinal inflammation		10.81(-33.45,55.07)	0.62
	Arterial intimal fibrosis		29.97(-12.72,72.67)	0.16
	Arterial hyalinosis		-39.08(-228.56,150.33)	0.68
	Glomerular thrombi		-30.41(-88.54,27.73)	0.30
	Acute tubular injury		-5.09(-22.56,12.63)	0.56

In our study, no statistically significant relationship was found between the zero-time histopathological findings after the adjustment of other variables, with the graft function and survival. Although some Histopathological findings are more associated with DGF, they were not statistically significant.

The results of various studies and reviews about the clinical importance of zero-time biopsy are very contradictory and controversial. Some researchers consider zero-time biopsy to be useful only to predict the function, especially in the first month and year after transplantation, as well as to compare with subsequent biopsies, and they hope that changes in the immunosuppressive treatment after transplantation can improve survival. Some people only consider it a research role. Whereas others also find it useful in marginal kidney grafts and mention that, it is possible to reduce the amount of discarding of donated organs, especially considering their scarcity (5, 6).

In 2007, El Husseini et al., confirmed the predictive role of abnormal biopsy findings in determining prognosis. They examined 16 studies including 8122 kidney transplants, six of which were prospective studies. Histopathological abnormalities were classified by the Banff scoring system. In general, abnormal time zero

Table 2. Correlation between changes in serum creatinine levels with possible predictive factors

Variables	Categories		β(95%CI)	P-value
Time	Time 0		Ref.	
	Time 1		-5.91(-6.41, -5.41)	0.00
	Time 3		-6.05(-6.55, -5.55)	0.00
	Time 6		-6.07(-6.58, -5.57)	0.00
Sex	Female		Ref.	
	Male		.93(-.87,2.74)	0.31
Age			-.005(-.072,.06)	0.86
BMI			.083(-.10,.27)	0.39
Comorbidity	Without		Ref.	
	HTN		.052(-1.73,1.84)	0.95
	DM		-.31(-3.3,2.67)	0.83
	HTN/DM		-.17(-4.71,4.36)	0.94
	HTN/DM/CVA		-1.97(-6.61,1.67)	0.29
CPR	No		Ref.	
	Yes		-.73(-3.41,1.95)	0.54
Cause of Brain Death	ACCIDENT		Ref.	
	ALCOHOL		.86(-3.54,5.26)	0.70
	BRAIN TUMOR		-.86(-3.35,1.63)	0.49
	FALLING		-.06(-2.53,2.41)	0.96
	ICH		.02(-2.30,2.34)	0.98
	SIEZURE		.05(-4.29,4.40)	0.97
	SUICIDE		.54(-1.50,2.58)	0.52
	TOXICITY		.09(-4.06,4.25)	0.96
Histopathology	Number of glomeruli		-.00(-.04,.04)	0.97
	Globally sclerosed glomeruli		-1.08(-3.88,1.70)	0.44
	% of global glomerulosclerosis		.24(-.10,.59)	0.176
	Number of arteries		.99(-2.53,4.52)	0.58
	Intristial fibrosis	Mild	-.71(-3.67,2.24)	0.63
		Moderate	-1.06(-4.34,2.21)	0.52
	Intestinal inflammation		.03(-3.64,3.72)	0.98
	Arterial intimal fibrosis		-1.21(-4.77,2.33)	0.50
	Arterial hyalinosis		-4.08(19.84,11.68)	0.68
	Glomerular thrombi		-.02(-4.86,480)	0.99
	Acute tubular injury		-.19(-1.64,1.25)	0.79

biopsies were better predictors of early graft performance. In some special cases, such as an older donor kidney, people with a history of DM, HTN, cardiovascular disease, and abnormal creatinine, zero-time biopsy has a significant prognostic value. However, more studies are needed to evaluate the value and practicality of zero-time biopsy regarding long-term function (2).

In 2008, Mancilla E et al., investigated the predictive value of vasculopathy involved in time zero biopsy. Short-term graft survival does not appear to be associated with suboptimal histology. If the vasculopathy is evident during transplantation, the possibility of impaired kidney function increases in the first week and 3 months after transplantation. Long-term graft survival is inversely related to the severity of arteriosclerosis. Although the results of other studies are contradictory, it can be said that vasculopathy is one of the main factors in short-term and long-term survival (7).

In 2010, Cockfield SM et al., studied 730 zero-time biopsy samples. Independent risk factors of DGF included re-transplantation, longer cold ischemia time, and HLA-DR mismatch. Age was not a risk factor for DGF. Among

the histopathological findings, arteriolar hyalinosis is independently associated with DGF and graft loss. While intimal fibrosis was associated with decreased kidney function in 6 months, the severity of glomerulosclerosis was not related to survival and clinical outcomes (8).

In 2015, Lee et al., reviewed the importance of time zero biopsy. According to his research, the suitability of renal allograft for transplantation from a brain-dead donor requires consideration of the clinical condition of the donor and the histopathological condition of the donated kidney (9).

Meanwhile, in 2015, Yagi Sawa et al., reported after examining 483 transplanted kidney biopsy samples that the presence of arteriosclerosis in zero-time biopsy samples is a risk factor for tacrolimus-induced nephrotoxicity (10). Conversely, more recent studies have not found significant benefits in terms of rejection rates, graft survival, or renal function, and suggest that it should be reserved for high-risk patients for graft rejection (11-13).

More recently Mokos et al., in a study investigating the predictor factors for post-renal transplant anemia have found that time-zero kidney biopsy findings like the degree of glomerulosclerosis may be predictors of PTA (13).

Among the strengths of our study, the following can be mentioned: Biopsies at zero time after establishing perfusion (after de-clamping the artery). Many studies have been done before perfusion. However, for the limitations of the study, we can mention the small number of samples due to the COVID-19 pandemic and not considering some variables. Conducting this type of research requires a large-scale decision at the national level so that both the number of samples is large and long-term follow-up of patients is provided.

According to our results, it may be supposed that in non-marginal cases, the microscopic evaluation of the zero-time biopsies currently does not have a clear clinical significance and this is worsened by the lack of a precise zero-time biopsy protocol. Molecular investigation of the zero-time biopsy specimens is a new field that may give us more effective information.

Conclusions

Although it was not statistically significant, more glomerulosclerosis and a higher degree of interstitial fibrosis were associated with more DGF, and this has been confirmed in previous studies. But the noteworthy point is that the kidneys with inappropriate zero-time biopsy showed good performance, and this indicates that based on histopathological findings, the patient should not be excluded from marginal samples and be denied dialysis.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no conflict of interest.

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Ethics statement

All patients entered the study after completing an informed consent form, and this study was registered with the ethics committee under code IR.TUMS.MEDICINE.REC.1398.342.

Data availability

Data will be provided on request.

Abbreviations

DGF	Delayed graft function
ATN	Acute tubular necrosis
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
RRT	Renal replacement therapy

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