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Investigation of serum levels of Tacrolimus in Iranian renal transplants in 2014 – 2015

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ABSTRACT

To date 24000 kidney transplantations has been performed in Iran. In this study we enrolled different groups of transplanted patients that received immunosuppressive drugs after surgery. It is necessary that doses used for patients be proportionate to patient's immune system potential. One of the currently known immunosuppressive drugs is tacrolimus (prograph) and most patients well tolerate the drug in levels of 5-20ng/ml. Proper therapeutic limit of drug depends on kind of transplantation, test protocol and instructions. Therapeutic effects may depend on sampling time (immediately before timing dose). In other times the results will rise. This is the first study in Iran on serum levels of tacrolimus in transplanted patients in 2014-2015 according to cardiovascular and biochemical factors of patients. Study was descriptive-honorific and population study chose from patients referred to Ttacrolimus Measurement Center and tests were done by ABBOTT ARCHITECT system that uses chemilumine scence mechanism. In this study we evaluated 1193 patients that 192 of them monthly referred to Tacrolimus Measurement Center. Blood samples (5ml) took from each patient. Data gained about FBS had direct correlation with tacrolimus levels in diabetic patients, but had reverse relation with their HCT. Mean effective serum level of tacrolimus in adult patients without background disease was 1.4-5 ng/ml, in diabetics was 5-14 ng/ml and in children under 15 had fluctuation (0.9-2 ng/ml) after first dose. GFR had not significant relation with levels of creatinine, urea, drug level and liver enzymes. In other hand, serum levels of drug had significant correlation with transplantation duration. To prescribe tacrolimus doses we should consider background diseases e.g. diabetes and nutrition status of patients. This study done for the first time in Iran and suitable dose for adult patient determined as 1.4-5 ng/ml. we suggest that future studies consider genetic factor evaluations in their design study.

KEYWORDS: FBS, ABBOTT ARCHITECT, HCT

INTRODUCTION

By developing new curing technologies like organ transplantation and transplant maintenance by immunosuppressive drugs such as Tacrolimus, Sirolimus, Cyclosporine, etc., a new horizon in improving treatments has been flourished. An allograft transplanted organ next to main molecules (called Major histocompatibility (MHC)) is considered as an alien agent by recipient's immune system. Donor's organ carrying different tissue antigens, is recognized by recipient's microphages and sent to lymphocytes. Afterwards, various lymphocytes start to produce and secret different lymphokines which attack transplanted organ and cause organ damage. Immunosuppressive drugs control recipient's immune system responses and prevent transplant rejection. Acute transplant rejection is, in fact, a sign of chronic transplant rejection, which is considered as one of the most prevalent reasons of transplant failure.

Nowadays, the basic problem in organ transplantation is to protect transplanted organ against immune system. Unfortunately, immunosuppressive drugs act as a double-edged sword and by increasing drug's serum level, vulnerability to opportunist infections or cancers is more likely [1]. This indicates the importance of therapeutic limits of immunosuppressive drugs prescribed to renal transplant patients.

There are various kinds of these drugs that each has advantages and disadvantages. Most of the small immunosuppressive molecules with medicinal role are originated from microbial products and target proteins which are highly protected in evolutionary path. Cyclosporine and rapamycin (sirolimus) are examples of these drugs. A recently developed and used drug in Iran is tacrolimus. Since these drugs are not effective in clinically tolerable concentrations, the main challenge is to obtain an effective level of immune suppression which prevents transplant rejection with the least side effect. KDIGO (Kidney Disease Improving Global Outcomes) is a renal diseases monitoring organization which checks the disease growth worldwide. This organization has suggested Tacrolimus as

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a pioneer calcineurin inhibitor along with an anti-propagation agent with or without corticosteroids for primary treatments and preservations [2].
Tacrolimus inhibits calcineurin's activity; however, practically, it just inactivates a part of calcineurin's activity [3] which makes the drug effects dependent on its concentration (competitive). As a result, applied dose and also patient's situation have to be considered when using these drugs which, sadly, are not considered enough in Iran. We are trying to determine the drug effects and effective serum levels in transplant patients by measuring effective serum levels on patients and their biochemical parameters including urea, creatine, sodium and potassium (kidney checking factors), aspartate amino transferase (SGOT (AST)) and Alanin amino transferase (SGPT (ALT)) (liver tissue checking factors) and hematocrit (HCT) and variation coefficient of red cell size (RDW) (hematological factors). Data and results of this study have been statistically analyzed using SPSS software, version 19.5.

Rental transplantation

One of the most important treatments for an organ's dysfunction is transplantation. Renal transplantation is used as a treatment for most patients suffering from acute renal insufficiency. Transplanted kidney is obtained from a healthy donor or a brain dead individual. Before transplantation surgery, a series of tests, like blood group similarity between donor and recipient, are conducted to lessen any probability of mistake or renal transplant rejection. In most cases, transplanted kidney starts its activity immediately after the surgery. Sometimes, however, suitable function may delay some days, a case in which hemodialysis can be used until a desirable function of kidney in met. When a recipient has received the kidney in his/ her body [4,5], immunosuppressive drugs are applied to decline acute transplant rejection. However, chronic and long-term use of these drugs results in not only life-threatening infection, but also cancer risk [6].

Immunosuppressive drugs have three impacts: preventing transplant rejection (therapeutic effect), preventing the side effects of immunosuppressive diseases (like infection or cancer), and having non-immune toxicity for other tissues [7]. Recent studies have shown due to a new nephropathy infection by virus BK (related to polyoma), lymph proliferative disorder has been seen more [1]. This syndrome, observed in tubular damage, is caused by a virus, usually harmless for healthy individuals, as a result of immunosuppressive drugs use to prevent transplant rejection.

MATERIALS AND METHODS

Measuring serum level of tacrolimus was conducted during September, 2013 till September, 2014 in Aramesh laboratory, the only center measuring Tacrolimus serum levels by ABBOTT–Architect device, out of charge. Besides, various biochemical and hematological tests, like urea, creat, SGOT, SGPT, NA, K, Ca, K, FBS and blood parameter (RDW) and hematocrit (HCT) were done on referred people.

Applied Materials and devices

Materials

1.	Tacrolimus Kit	provided from ABBOTT Co. America
2.	Tacrolimus Precipitation Solution	provided from ABBOTT Co. America
3.	Tacrolimus Control Kit	provided from ABBOTT Co. America
4.	Tacrolimus Calibrator Kit	provided from ABBOTT Co. America
5.	Blood Sugar Monitor Kit	provided from Pishtaz Teb Co., Iran
6.	Urea Assay Kit	provided from Pars Azmoon Co., Iran
7.	Creatine Assay Kit	provided from Pars Azmoon Co., Iran
8.	SGOT (AST) Assay Kit	provided from Pishtaz Teb Co., Iran
9.	SGPT (ALT) Assay Kit	provided from Pishtaz Teb Co., Iran
10.	Calcium Level Assay Kit	provided from Pishtaz Teb Co., Iran
11.	Phosphorus Level Assay Kit	provided from Pishtaz Teb Co., Iran
12.	Sodium Electrode	
13.	Potassium Electrode	
14.	SERONORM, Pathonorm Control Kit	
15.	ELICAL Calibrator	

Devices and tools

1.	Auto analyzer device	ABBOTT i1000SR
2.	Auto analyzer device	MINDRAY BS 380
3.	Hematology auto analyzer device	NIHONKODEN CELL E

4.	Auto analyzer	SENSA CORE ST200M
5.	Refrigerated centrifuge	HETTICH UNIVERSAL 320 R
6.	Venoject syringe	provided from Tajhiz Andish Co.
7.	Venoject needle	provided from Tajhiz Andish Co.
8.	Vacutainer CBC tube (lavender-top, containing EDTA)	
9.	Vacutainer coagulation tube (red-top)	
10.	ABBOTT – specific cup	
11.	ABBOTT – specific micro tube	
12.	ABBOTT – specific TRIGGER, PRETRIGGER solution	
13.	ABBOTT – specific RV cup	
14.	HITACHI cup, for auto analyzer device MINDRY and ACHIHIT	
15.	Yellow sampler tip 200µl	
16.	Blue sampler tip 1000 µl	

Sampling method

Samples were taken from patients of contractual hospitals in different times of days and nights under specific conditions, and referred to our center after coding. Related authorities had been asked to put 5cc of specimens in lavender-top or Pink-top tubes containing EDTA K2 or K3, reserve them at room temperature and send them to our center. After specimens were delivered to our laboratory reception, patients' names were matched with their companion papers, consumed dose were registered and it entered the reception system. Then specimens with their labels, indicating patient's name, reception number and related test, were delivered to sampling section wherein a person controlled the specimens for coagulation and correct sampling. Confirmed specimens received their labels and were referred to the related section.

It's worth mentioning during these investigations we realized if specimens are hemolyzed or put in tubes except lavender-top CBC tubes (EDTA), we will have false results.

We remind those who came for tacrolimus level measurement that there's no fasting requirement for this test and the test should be done 8-10 hours after consuming this drug. Then, they were referred to laboratory reception where they present their personal information, like age, gender and time of their renal transplantation and also dose of received prograf drug. This personal information is then registered in reception section and sent to sampling section along with a label indicating measurement of other parameters including blood and biochemical parameters on the request of the related doctor.

Monoject sampling was conducted, and some blood was poured in red-top vacutainer coagulation tube which was put in room temperature in order that clot is formed. Afterwards, blood serum was separated using 4000 rpm centrifuge. This process was repeated, if necessary, to obtain a complete serum separation. This serum was then poured into a gamma tube, having a label of personal information, and sent to the other unit for biochemical parameters measurements, like urea, creatinine, etc. Furthermore, two blood CBC specimens (5 cc) in lavender-top tubes (EDTA) were taken simultaneously which were shaken upside-down for several times to prevent coagulation forming and to mix with EDTA. Next, one of these specimens was sent to hematology unit and the other to hormone ABBOTT ARCHITECT unit.

Data analysis and statistical method

Data were analyzed by descriptive method using statistical software, SPSS version 20, and graphs were plotted. Level of confidence was 95%.

RESULTS AND DISCUSSION

Populations and type of study

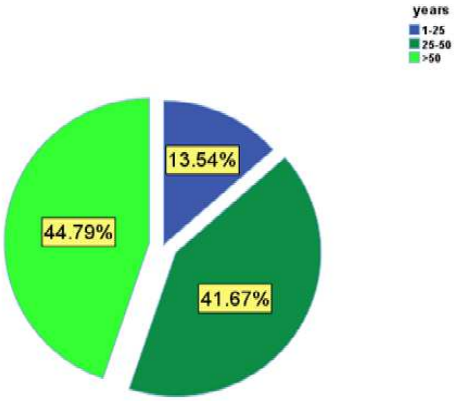
The present study is sociology descriptive (HSR) that has done on 1193 renal transplant patients referring to Aramesh laboratory during September 2013 till September 2014. On average, 10 samples were monthly taken from 192 patients during one year from September 2013 till September 2014. Complete period of tacrolimus serum level investigation had been done on these patients who willingly had provided us with their transplantation information. Both serum levels of this drug and blood and biochemical parameters were assessed on these people.

Categorizing patients according to their age and gender

Patients were categorized into three age groups 1-25, 25-50 and more than 50 years old from which, as its clear in the following graph, 41.67% (80 samples) and 44.79% (88 samples) belonged to the group of 25-50 and more

than 50, respectively. Average age of patients was 46.68 ± 13.8, and the youngest and oldest people were 8 and 71 years old, respectively.

In the case of gender, 34.4% (66 people) were female while 65.6% (126) were male. No significant statistical difference was observed in tacrolimus level (p=0.001) between two genders.



Graph 1- categorizing patients according to their age and gender

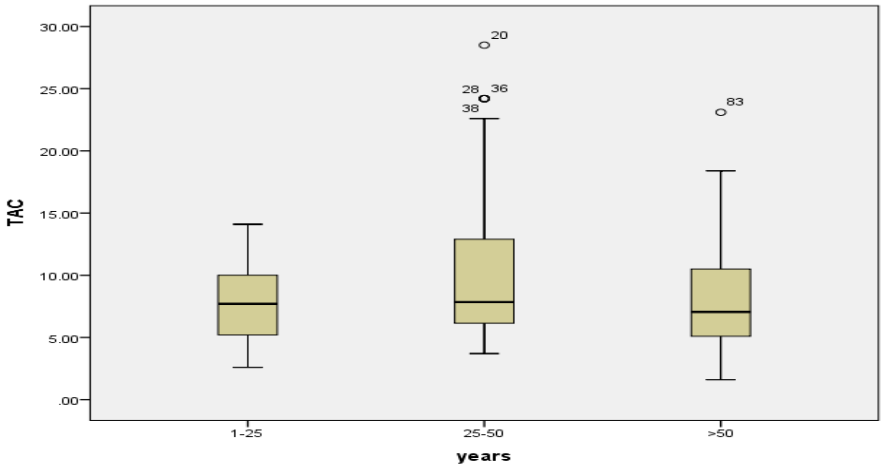
Results of Tacrolimus level measurement
Descriptive statistics

Table 1- Tacrolimus levels

	N	Minimum	Maximum	Mean	Std. Deviation	Variance
Years	192	21	71	46.68	13.800	190.440
TAC	192	1.60	28.50	8.9870	5.09544	25.964
Valid N (listwise)	192					

Tacrolimus level in different age groups

Tacrolimus level in different age groups can be seen in the following graph which demonstrates that the highest level of Tacrolimus is observed in 25-50- year- old patients.



Graph 2- Tacrolimus levels in different age groups

Tacrolimus serum level in different age groups

The averages of drug level were 2.88 ± 2.15 in the group of less than 25 years old (confidence interval 95%, 4.15-0.9) and 10.49 ± 6.11 in the group of 2-50 years old (confidence interval 95% in 11.85-9.13) in which the least and the most amount of drug in blood was 3.7 and 28.50 µg/l, respectively. Average amount in the age group of more than 50 was 7.92 ± 4.11 (confidence interval 95%, 8.8 – 7.03) for which the least and the most level was 0.09 and 23.10 µg/l, respectively.

Results were not significant in age groups of less than 25 years old and more than 50 years old; however, age group of 25-50 years old was significant (P value: 0.34).

Table 2- Tacrolimus serum level in different age groups

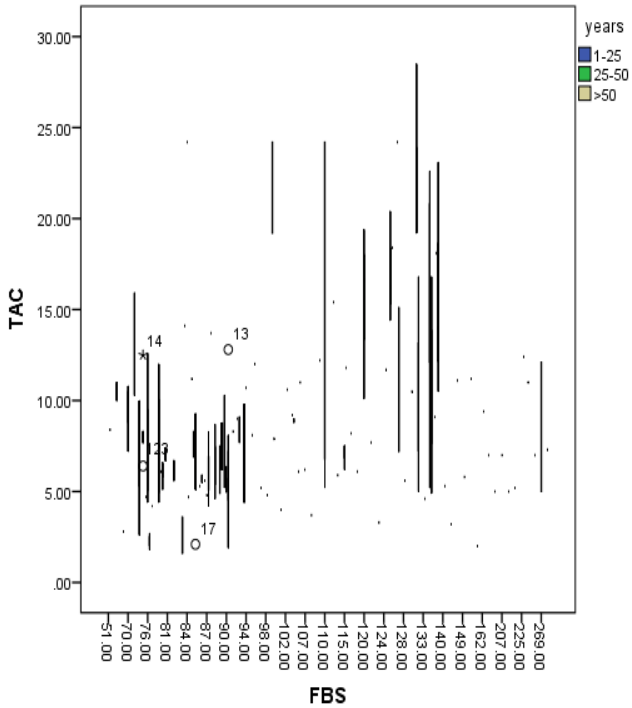
Age group	N	Mean	Std. Deviation	95% Confidence Interval for Mean		Minimum	Maximum
				Lower Bound	Upper Bound		
1-25	26	2.8808	3.15062	1.6082	4.1533	0.90	14.10
25-50	80	10.4925	6.11985	9.1306	11.8544	3.70	28.50
>50	86	7.9209	4.11774	7.0381	8.8038	1.60	23.10
Total	192	8.9870	5.09544	8.2616	9.7123	0.90	28.50

Relation between tacrolimus and biochemical parameters

Results of Biochemical parameters, fasting blood sugar (FBS), liver enzymes (SGOT, SGPT), creatinine, urea, sodium and potassium had shown.

Fasting blood sugar (FBS)

In all three mentioned groups, if non-diabetic patients are analyzed separately, there will be no significant difference between tacrolimus serum and blood sugar levels; however, it was seen that serum level of drug in diabetic patients was more than other patients.



Graph 3- FBS changes with different Tacrolimus levels

Liver parameters (SGOT-SGPT)

According to liver parameters in the studied population, SGOT levels were not different from tacrolimus levels and followed a normal curve. However, although SGPT levels were not significant in each group (p = 0.0001),

analysis in two age groups, especially 25-50 years old and the other group, showed that Tacrolimus levels in blood is more ($p = 0.09$).

Sodium (Na) and Potassium (K)

A statistical relation between K and Na and tacrolimus increase was observed in ANOVA analysis. By increasing tacrolimus, blood sodium level goes up (although a little). However, the relation is negative between potassium and tacrolimus levels.

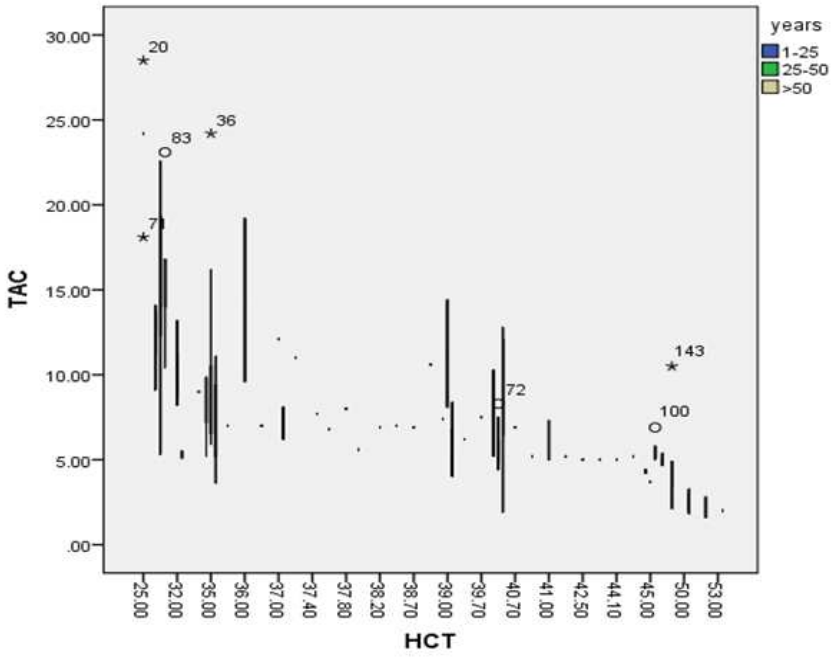
Results of blood parameters comparison

Hematocrit (HCT)

In all three categorized age groups, tacrolimus serum levels were negatively related to Hematocrit level (HCT) which is demonstrated in graph 4. By increasing the amount of Hematocrit, tacrolimus level declines.

Coefficient of variantion in Red-cell measurement (RDW)

Generally, in all ages, there is a significant relation between tacrolimus level and blood RDW ($p=0.37$) (Table 4).



Graph 4- Relation between Tacrolimus serum and Hematocrit (HCT) level

Results of other hematology and biochemical parameters are shown in table 4.

Table 3- Results of other hematology and biochemical parameters

Descriptive Statistics					
	N	**Mean**	**Std. Deviation**	**Minimum**	**Maximum**
TAC	192	8.9870	5.09544	0.90	28.50
FBS	187	106.8930	39.23734	51.00	290.00
SGOT	184	12.4212	4.73216	3.00	29.00
SGPT	184	17.9701	10.28012	3.00	48.00
HCT	159	37.4503	6.26762	25.00	53.00
RDW	158	15.5816	3.86580	10.00	46.00
Cr	165	1.7775	.84501	1.00	5.00
K	122	5.0672	4.24911	3.00	41.10
Na	109	140.0826	1.31324	136.00	145.00
Ur	126	60.9127	33.83561	20.00	200.00

Statistical analysis

Table 4- statistical analysis
ANOVA

		Sum of Squares	df	Mean Square	F	Sig.
SGOT	Between Groups	242.866	2	121.433	5.701	.004
	Within Groups	3855.121	181	21.299		
	Total	4097.987	183			
SGPT	Between Groups	8455.201	2	4227.601	70.302	.000
	Within Groups	10884.384	181	60.135		
	Total	19339.586	183			
RDW	Between Groups	29.387	2	14.694	.983	.377
	Within Groups	2316.889	155	14.948		
	Total	2346.277	157			
Cr	Between Groups	10.044	2	5.022	7.599	.001
	Within Groups	107.059	162	.661		
	Total	117.103	164			
K	Between Groups	60.496	2	30.248	1.695	.188
	Within Groups	2124.152	119	17.850		
	Total	2184.649	121			
Na	Between Groups	.873	2	.436	.250	.780
	Within Groups	185.384	106	1.749		
	Total	186.257	108			
Ur	Between Groups	21721.867	2	10860.934	11.006	.000
	Within Groups	121384.172	123	986.863		
	Total	143106.040	125			

Conclusion

Corticosteroids affect bone marrow and reduce number of immune cells which causes patients to be infected by various elements, especially viral ones like cytomegalovirus (CMV). So, tacrolimus which not only controls immune system, but also removes any needs to corticosteroids helps transplant survival and patient's normal life [13].

According to studies, tacrolimus effective level differs in various societies with regard to genetic and life-style differences [9, 15].

The effective serum level of tacrolimus in this study averaged 8.99 mg/l with 5.09 interval of variation which varied among age groups. According to gathered questionnaires in which the last consuming time was mentioned, and checking drug level of tacrolimus, the best time for measuring this drug's level was 8-10 hours after last consumption.

Studies of Fitzsimmons *et al* on Tacrolimus serum levels indicated there is no significant difference between different genders [9]. Our research has shown no significant difference between genders and serum levels, as well. Nevertheless, Kupers *et al*., concluded renal transplant females, compared with males, had higher concentrations of this drug. Results of the study done by Velckovic-Radovanovic R *et al* in 2012 on the influence of tacrolimus on peoples' gender demonstrated that the effects of tacrolimus differed according to gender. They witnessed penetration of corticosteroid and tacrolimus in males was more than that in females [16].

Time after transplantation has a significant effect on tacrolimus concentration, which fluctuated at the beginning of treatment with tacrolimus. This kind of fluctuation has been seen by several researches including Po *et al* who, doing a research on 50 renal transplant adults, observed a decline in drug dose in one to three months after transplantation [12].

In our study, there was just one patient younger than 15, and the number of patients in age group of less than 25 was less than other groups which led to results different from what was seen by Jain *et al.*, (1991) who witnessed tacrolimus level in children was 1.8 times more than that in adults [10]. A reason for this may be more entry of drug into red globules and fewer plasma proteins, attached to drug, in children. However, as observed in a recent study by Venkateramenan *et al*, (1995) drug levels were identical in both. In the present study, no significant difference was seen between children and adults more than 50, whereas the difference with the age group of 25-50 was significant (P=0.34) (graph 1).

Although studies have shown that there is no significant relation between tacrolimus and blood sugar [14], it has been seen in diabetics that high levels of tacrolimus not only is needed for treatment, but also may increase blood sugar. The amount of tacrolimus in this research (graph 3) is higher in those having blood glucose more than 110 mg/dl. This can be due to attachment of tacrolimus to sugar which results in its deactivation; consequently, more level of drug is required.

Tacrolimus metabolism pathway goes through liver which makes us expect those with liver dysfunction to have more tacrolimus concentration in their blood. In this study, there was no significant difference between the levels of tacrolimus and liver enzymes SGOT and SGPT (p= 0.0001); however, in age group of 25-50, the amounts of SGPT and tacrolimus were different in confidence interval of 95% (p= 0.09). This may be due to high number of patients in this group or toxicity effects of corticosteroid drugs (and even Tacrolimus, when consumed dose is more than drug toxicity level). To date, no significant relation has been reported between creatinine serum level and tacrolimus clearance. Patients with acute renal failure and dialysis patients had tacrolimus clearance similar to healthy people [8]. Findings of our study confirm those of other researches, and show no significant difference between tacrolimus serum levels and kidney activity parameters, including creatinine and urea (P= 0.001).

As it's demonstrated in graph 4, increasing hematocrit levels causes tacrolimus levels to decrease. It's obviously because of tacrolimus tendency to attach to red cells (not hemoglobin) which is influential in its stability and bioavailability. Undre *et al*. have presented the same results [17]. On the other hand, Ghoshal *et al* believe that the reason is its attachment to albumin and red cells and has no effect in concentrations more than 9 ng/ml [18].

RDW, a factor indicating RBC normality, has a significant relation with tacrolimus serum level (P= 0.37) in renal transplant patients regardless of age (Table 3). It can be justified by considering tacrolimus attachment to RBC and forming various shapes with natural kind of red cells.

Amounts of sodium and potassium are of effective factors in diseases which, indeed, have lots of fluctuations in renal patients. However, after renal transplantation and having successful renal activity, these two factors are considered as controlled parameters in patients and play a role in both heart and vessels activities. In this study, potassium level was negatively related to tacrolimus level (P= 0.18) and positively related to sodium (P=0.78). This change, averages 5.07, is tiny in case of potassium which is due to decline in renin and aldosterone levels because of kidney inability in maintaining the level of these elements. Increasing sodium level can explain high blood pressure in patients consuming tacrolimus.

Conclusion and suggestions

According to what we have mentioned so far, it can be concluded that although various suppressive drugs with different functional mechanisms, advantages and disadvantages are applied in organ transplantation, calcineurins, especially tacrolimus, are the main base in transplantation maintenance and immunosuppression which reduce acute transplantation rejection. However, Improve long-term graft survival which consequently leads to increase drug interaction and complexity, and according to instant clinical recognition, therapeutic drug monitoring and dose adjustment becomes the matters of importance. Another considerable issue is calcineurin inhibitors have a limit therapeutic window, and their effective dose is the one causing toxicity, and changing drug's dose have serious consequences, that's why reaching a suitable dose is often challenging in practice. This is due to different effectiveness of the drug in different patients or even in one. In particular, after applying one dose of a calcineurin inhibitor, its blood concentration in different patients changes considerably. As a result, to obtain a desirable result, therapeutic drug monitoring (TDM) and therapeutic monitoring index is highly important. Most of doctors who prescribe calcium inhibitors measure drug's blood level to reach a suitable dose. Usually, measuring blood concentration at the time of prescribing tacrolimus and then presenting the results to nephrologists is the basis of cure in each patient, and is an approach which decreases costs for patients and prevents side effects of changing therapeutic dose of tacrolimus.

Based on the results, we suggest investigating expression of gene P450 and its mutation, besides mentioned factors, to make not only biochemical elements, but also genetic factors involved in tacrolimus metabolism clear.

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