Original Research Paper

Volume - 14 | Issue - 01 | January - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Surgery

COMPARATIVE STUDY OF THE SERUM TISSUE PLASMINOGEN ACTIVATOR(T-PA) LEVELS IN DIABETIC PATIENT WITH AND WITHOUT FOOT ULCER.

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ABSTRACT **Background:** Diabetic foot ulcer is associated with significant microangiopathy which causes damage to the vascular endothelial cells leading to increased risk of thrombus formation along with impaired process of fibrinolysis. tPA is the most important part of the fibrinolytic system. It has been proven that the level of tPA in the blood reflects fibrinolytic activity. Hence t-PA levels can be used to identify patients who have microangiopathy and are at risk of developing diabetic foot ulcer. **Objective:** To compare the concentration levels of serum tissue plasminogen activator (t-PA) levels in Diabetic patients with and without foot ulcer. **Materials and methods:** This study was conducted in the Department of General Surgery during the period October 2017 to May 2019. Serum Tissue plasminogen activator (tPA) levels in Diabetic patients with and without foot ulcer were assessed and compared. All the demographic parameters studied were also compared with mean tPA and their significance were analyzed. **Results:** A total of 85 patients with Diabetic foot ulcer and 85 Diabetic patients without foot ulcer were recruited in the study. Median tPA levels (ng/ml) in a diabetic patients with and without foot ulcer was 3.7 and 4.6 with a statistical significance (p value=0.005). Mean tPA levels in patients who presented with and without gangrene among ulcer group was 3.17 ± 1.05 and 4.52 ± 1.69 respectively(p value<0.001). Mean tPA levels in ulcer group who had Wagner's grade of ⩽2 and >2 were 5.87 ± 1.79 and 3.51±1.09 respectively. (p value<0.001). **Conclusions:** Tissue plasminogen activator (t-PA) concentration is significantly lower in diabetic patients with foot ulcer. Lower concentration of t-PA is associated with microangiopathy complications like foot gangrene and higher Wagner's grade

KEYWORDS : Diabetic Foot, Tissue Plasminogen Activator, Microangiopathy.

INTRODUCTION:

Diabetic patients are more susceptible to develop foot ulcers due to various reasons. Hyperglycemic state in diabetes contributing to foot ulcers could be due to peripheral arterial disease, peripheral neuropathy, and immunosuppression.[1] Diabetic foot ulcer occur in the setting of significant microangiopathy. Studies have shown that diabetic patients are more prone to develop endothelial dysfunction and impairment in the process of fibrinolysis[2]. This procoagulant state in diabetes potentiates microthrombus formation and leads to the progression of atherosclerosis.[3,4] The primary function of Tissue plasminogen activator (tPA) is to convert plasminogen into plasmin which is considered to be the key enzyme in dissolving clots. The levels of Tissue plasminogen activator (tPA) antigen are found to reflect the endothelial dysfunction.[3,4] There are many publications available on tPA activity and its levels on various conditions like stroke and myocardial infarction but there are very few published data available on the effect of tPA over the pathogenesis of diabetic foot ulcer. [5] In this study, we have compared the levels of t-PA antigen in diabetic patients with and without foot ulcer.

MATERIALS & METHOD:

This cross sectional comparative analytical study was conducted from October 2017 to May 2019 in the Department of General Surgery in a tertiary care hospital after getting approval by the Institute Ethics committee (JIP/IEC/2017/0168).

All Patients more than 18 years of age with diabetic foot ulcer were included in group 1 (DFU) and diabetic patients more than 18 years of age without healed or active foot ulcer without infection were included in group 2(DM). Patients having history of myocardial infarction or cerebral stroke treated with thrombolysis within last 6 months, pregnant females and patients on antiplatelets or fibrinolytics were excluded.

Demographic data, clinical details of diabetes, treatment and foot examination details were collected from both the groups. Laboratory details like Fasting blood sugars (FBS), HbA1c, Total leukocyte count, total proteins and albumin were collected from patient data. Blood sample for Tissue plasminogen activator (t-PA) assay was collected between 7 and 9 AM on an empty stomach from participants in both groups. The concentration of Tissue plasminogen activator (tPA) was estimated using the Enzyme Linked Immunosorbent Assay (ELISA) method. Levels of Tissue plasminogen activator (tPA) in both groups were compared.

Sample size calculation

The sample size was estimated using OPENEPI® software version 3. The sample size was estimated with a minimum expected difference in mean for tPA level between the two groups as 3.46 with a standard deviation of 6.92. The sample size was estimated as 85 in each group at 5% level of significance and 90% power.

Statistical Analysis:

The descriptive statistics include frequencies, proportions, and percentages for categorical variables while the continuous variables were analyzed and explained in terms of mean and standard deviation. Other measures of central tendency and variation like median were analyzed wherever applicable. The inferential statistics was explained based on the application of statistical test to find out the significant difference in proportions by Chi-square test. For continuous variables in the form of scores a significant difference of mean score with other parameters of importance was done either by t-test or Mann-Whitney U test. Moreover, advanced statistics i.e. regression analysis was done to assess for t-PA level with other parameters as predictors of microvascular complications. The results were explained if there is any significant difference found at the 95% significance level wherever required and applicable with $p<0.05$ between the two groups.

RESULTS:

A total of 170 patients were included in this study with 85 patients each group. Mean age and Gender distribution were comparable between the groups. Prevalence of smoking was higher in diabetic foot ulcer group as compared to ulcer group (31.8% vs 28.2%), however the difference was not statistically significant. Duration of diabetes in majority of the patients was less than 10 years in both the groups(87.1% and 88.2%). (Table1)

Table 1: Comparison of demographic characteristics between Diabetic patients with and without foot ulcer (N=85 in each group)

		Diabetic with foot ulcer		Diabetic without foot ulcer		P Value
		N	%	N	%	
Age (Years)	21 to 30	1	1.2%	1	1.2%	NA
	31 to 40	11	12.9%	11	12.9%	
	41 to 50	9	10.6%	9	10.6%	
	51 to 60	34	40.0%	34	40.0%	
	61 to 70	27	31.8%	27	31.8%	

	71 to 80	3	3.5%	3	3.5%	
Gender	Male	53	62.4%	53	62.4%	NA
	Female	32	37.6%	32	37.6%	
Diabetes treatment	Insulin	17	20.0%	13	15.3%	0.221*
	OHA	62	72.9%	70	82.4%	
	No treatment	6	7.1%	2	2.4%	
Smoking	Yes	27	31.8%	24	28.2%	0.616*
	No	58	68.2%	61	71.8%	
BMI (Kg/m2)	<18.5 (Under nutrition)	3	3.5%	3	3.5%	0.715*
	18.5 to 22.9 (Normal)	74	87.1%	70	82.4%	
	23.0 to 24.9 (Overweight)	7	8.2%	9	10.6%	
	>25.0 (Obese)	1	1.2%	3	3.5%	
Duration of Diabetes (years)	<10	74	87.1%	75	88.2%	0.816*
	>/=10	11	12.9%	10	11.8%	

* Chi-square

Among the ulcer group, in ulcer was involving foot region alone in 57% of patients and was involving the leg region in 43% of patients. 31.8% of patients had an ulcer surface area of >100 cm^2 and 32.9% patients had gangrenous changes at presentation. 76.4% of patients presented with ulcer of Wagner's grade 2 or more. 76.5% of patients had negative probe to bone test. 64.7% patients did not have any bony involvement on x-ray assessment.

Table.2 shows the correlation of biochemical parameters in between both the groups. Mean value of HbA1C (%) in diabetic patients with and without foot ulcer was 8.9±2.4 and 7.8±1.9 respectively. (p-value-0.001). Mean value of Albumin (g/dl) in diabetic patients with and without foot ulcer was 2.6±0.7 and 3.3±0.8 respectively (p value<0.001). Mean value of TLC (per mm3) in diabetic patients with and without foot ulcer was 15325.0±8008.2 and 10308.9±4271.2 respectively(p value<0.001).

Table 2: Comparison of biochemical parameters in both the groups

Parameter	Diabetic with foot ulcer	Diabetic without foot ulcer	p value
	Mean±SD	Mean±SD	
FBS (mg/dl)	207.9±88	194.5±78	0.295*
HbA1C (%)	8.9±2.4	7.8±1.9	0.001*
Total Protein (g/dl)	6.4±1	6.6±1.1	0.158*
Albumin (g/dl)	2.6±0.7	3.3±0.8	<0.001*
TLC (per mm3)	15325±8008.2	10308.9±4271.2	<0.001*

* Independent t-test

Mean t−PA level(Mean±SD in ng/ml) in diabetic patients with and without foot infection was 4.07±1.63 and 5.35±3.20 respectively, which was found to be statistically significant (p value=0.001) by using the independent t-test. Median t−PA (ng/ml) in diabetic foot infection and without foot infection was 3.7(10.1) and 4.6(16.7) which was found to be statistically significant (p value=0.005) by using Mann Whitney U test.

On correlation of mean t−PA (ng/ml)levels with the demographic and clinical parameters in both the groups, presence of gangrene and ulcer with Wagner's grade >2 was showed statistical significance (p value<0.001). (Table 3)

Table 3: Correlation of mean tPA (ng/ml) with the demographic and clinical parameters in both the groups

Parameters		Diabetic with foot ulcer t-PA (ng/ml)			Diabetic without foot ulcer t-PA (ng/ml)			p value
		N	Mean		N	Mean	SD	
Age (Years)	<50	21	3.87	1.49	21	5.72	3.57	0.810*
	≥50	64	4.14	1.69	64	5.23	3.10	
Gender	Male	53	4.12	1.53	53	5.63	3.24	0.302*
	Female	32	4.00	1.81	32	4.89	3.13	
BMI(Kg/m2)	<18.5 (Undernutrition)	3	3.20	.71	3	5.11	1.43	0.557*
	18.5 to 22.9 (Normal)	74	4.13	1.71	70	5.50	3.43	
	23.0 to 24.9 (Overweight)	7	3.86	1.13	9	4.04	1.59	
	>25.0 (Obese)	1	3.57	.	3	6.12	1.68	
Duration of Diabetes (Years)	<10	74	4.10	1.67	75	5.27	3.07	0.748*
	≥10	11	3.86	1.45	10	6.02	4.22	
Smoking	Yes	27	3.71	1.61	24	6.30	3.52	0.476*
	No	58	4.24	1.63	61	4.98	3.02	
Diabetes treatment	Insulin	17	3.72	1.99	13	4.66	1.81	0.185*
	OHA	62	4.20	1.56	70	5.53	3.42	
	No treatment	6	3.70	1.25	2	3.78	1.57	
Gangrene	Yes	3.17±1.05						<0.001*
	No	4.52±1.69						
Wagner's Grade	≤2	5.87±1.79						<0.001*
	>2	3.51±1.09						

* Independent t-test

DISCUSSION:

In the present study the median t−PA levels in diabetic patients with foot ulcer was found to be significantly lower when compared to diabetics without foot ulcer (3.7 vs 4.6 ng/ml). The finding is concordant to a similar study done in Poland by Kulwas et al. The study showed lower median t−PA level in a diabetic with foot infection (4.95 vs 8.41).[5] The difference in t-PA levels in the both groups were high in the study by Kulwas et al as compared to the present study. This finding may be due to inclusion of patients with foot infection alone in their study. Presence of infection may falsely lower the levels of t-PA. In the present study all the ulcer with and without infection were included.

In the present study, we have done correlation analysis of serum t-PA levels with various demographic, clinical and blood parameters. None of the studies available so far has done a similar comparison. On subgroup analysis, we found that levels of t-PA correlated significantly with vascular complications like gangrene and higher Wagners grade ulcer. In our study mean tPA concentration of patients presented with foot gangrene is 3.17±1.05 and patients not having gangrene had t-PA of 4.52±1.69 respectively. This difference was found to be significant in our study. The possible explanation could be related to vasculopathy which causes disturbance of the fibrinolytic system that further leads to lower t−PA concentration.[5] In our study mean tPA concentration of patients having Wagner's grade ≤2 and >2 was 5.87±1.79 and 3.51±1.09 respectively. Kulwas et al compared t-PA levels with different Wagner's grade but it was found to be non-significant.[5] Our study has a significant association of t−PA with Wagner's grading.

The present study is not without limitations. Proportionate of patients with and without foot infection was not studied which could influence the levels of t-PA was not studied. Further studies are required to compare t-PA in advanced infection and sepsis.

CONCLUSION:

Based on the Tissue plasminogen activator (t-PA) concentration is significantly lower in diabetic patients with foot ulcer. Lower concentration of t-PA is associated with microangiopathy complications like foot gangrene and higher Wagner's grade.

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