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RESEARCH ARTICLE

Effect of Glycemic Control on Lipid Profile, Platelet Indices and Antioxidant Enzymes (Catalase and Superoxide dismutase) Activities in Type 2 Diabetics

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Abstract

The objective of present study was to determine the relationship of Glycemic control on lipid profile including ; Total Cholesterol, HDL ,LDL and Triglycerides) and on Platelet Indices (PLT, PCT, PDW, MPV) and to find effect of hyperglycemia on Antioxidant enzymes (Catalase and Superoxide dismutase) activities in type 2 Diabetic patients. This study was conducted on 30 Control and 50 Diabetic subjects. Blood sample of diabetic subject were collected from Baqai Institute of Diabetic and Endocrinology (BIDE) and were analyzed for fasting blood glucose, HbA1c, Total Protein ,Lipid Profile (Total Cholesterol, HDL ,LDL and Triglycerides,) Platelet indices (PLT ,PCT ,PDW ,MPV) and Antioxidant enzyme Catalase (CAT) and Superoxide dismutase (SOD). Result show that the blood glucose, HbA1c, Total Protein Total cholesterol, LDL and triglycerides were significantly increased in diabetic patient which is the sign of insulin deficiency, glycation of hemoglobin and a risk factor of cardio vascular diseases. Among Platelet Indices MPV and PDW were found to be significantly increased in diabetic patients as compared to control group. It is considered that alteration in platelet morphology and functions are associated with pathological processes and increased risk of vascular complications in patients with diabetes. Among Antioxidant enzyme activities; Catalase activity was found to be significantly increased in diabetic patient where as no significant variation was found in SOD activity. The high level of CAT is might to be due to compensatory mechanism against oxidative stress .The increase in the level of ROS in diabetes could be due to unbalancing between ROS generation and antioxidant enzyme status.

Introduction

Diabetes mellitus (DM) is a group of metabolic disorder characterized by abnormal carbohydrate metabolism resulting chronic hyperglycemia (high blood glucose levels) caused by defective insulin production or appropriate and efficient utilization of insulin by cells. This disease is spreading like epidemic all over the world.

Inappropriately managed diabetes cause severe complications The chronic, long term complications are related to blood vessel diseases and are generally classified into micro vascular disease (small vessel disease) such as those concerning the eyes(retinopathy), kidneys(nephropathy) and nerves (neuropathy) and; macro vascular disease concerning the heart and blood vessels (large vessel disease) (Jawa et al, 2004).

In hyperglycemic condition, when excessive glucose is present, the rate of glycolysis and the oxidative phosphorylation is amplified and the extra high energy electrons start to interrelate directly with oxygen molecules to produce superoxide which is very destructive in nature, and thus cause oxidative stress. Additionally, elevated blood glucose level is also a major factor in the development of diabetic complications. Recent studies have indicated that the unfavorable biochemical changes associated with hyperglycemia include increased flux of glucose.

Patients with type 2 diabetes mellitus have demonstrated the relation of both microalbuminuria and clinical proteinuria (Morgan, etal) with increased risk of mortality, which is largely due to cardiovascular diseases. Diabetes mellitus is a complex disease where the carbohydrate, Protein and fat metabolism are impaired (Altamer et al, 1991). Insulin affects many sites of lipid metabolism. It causes to stimulate synthesis of fatty acid in liver adipose tissue and in the intestine. The insulin has also been reported to increase synthesis of cholesterol (Jain et al, 1980). In the diabetes mellitus abnormal increased levels of lipid, lipoprotein and lipid peroxides in plasma may be due to the abnormal lipid metabolism (Suckling et al, 1993). It has been suggested that the increase in triglyceride may be due to insulin deficiency which results defective utilization of glucose that causes hyperglycemia and defective mobilization of fatty acids from adipose tissue (Shih et al, 1997). Alterations of lipid metabolism are an integral part of the metabolic syndrome and diabetes and can lead to the development of cardiovascular diseases (Nathan et al, 2005).

Platelets are essential for primary hemostasis and endothelial repair, additionally it also play a key role in atherogenesis and thrombus formation (De Gaetano, 2001). Epidemiological studies suggest that platelet indices are related to the risk of developing cardiovascular disease. Platelet count has also been associated with vascular and non-vascular death (Van der Bom et al, 2009) moreover recent studies showed that mean platelet volume is a predictor of cardiovascular risk (Chu et al, 2009); also Mean platelet volume (MPV) is a determinant of platelet functionality and increased MPV is associated with increased risk for myocardial infarction, stroke and transient ischemic attacks. Alteration in platelet morphology and function has been reported in diabetics and MPV was found to be significantly higher in diabetic patients (Papanas etal, 2004). Larger platelets are haemostatically more active and thrombogenic thus put the patient at a higher risk status for developing coronary thrombosis.

Oxidative stress is a condition in which oxygen free radicals especially reactive oxygen species (ROS) attack biological molecules such as lipids, proteins, and DNA. Free radicals are generated as by-products of normal cellular metabolism; on the other hand, various conditions are also known to disturb the balance between ROS production and cellular defense mechanisms. This imbalance can result in cell dysfunction and destruction resulting in tissue injury. Antioxidants are compound that protect cells against the damaging effects of reactive oxygen species, including thereby significantly delay or prevent oxidative damage. Antioxidant enzymes system comprises Catalase (CAT), Superoxide dismutase (SOD), Glutathione Peroxidase (GPX) and Glutathione Reductase (GR) enzymes whose activities contribute to eradicate superoxide, hydrogen peroxide and hydroxyl radicals provide natural defense system against free radicals. In recent studies, some evidence suggests that oxidative stress may play some important role in the etiology of diabetes and diabetic complications (Shinn, 1998).

Catalase is an antioxidant enzyme that catalyses the decomposition of hydrogen peroxide (H_2O_2) to H_2O and O_2. Hydrogen peroxide is produced in the eukaryotic cell as a by-product of various oxidase and superoxide dismutase reactions. H_2O_2 is extremely deleterious to the cell and its accumulation causes oxidation of cellular targets including DNA, proteins, and lipids leading to mutagenesis and cell death (Bai, et al, 1999) Removal of the H_2O_2 from the cell by catalase provides protection against oxidative damage to the cell. There is a relationship between the catalase and diabetes. In some studies Catalase level is significantly lower in diabetic patients suggested that autoxidation of glucose results in the formation of hydrogen peroxide (H_2O_2) which also enhances inhibition of antioxidant enzymes. Whereas In some studies Catalase level is significantly increased in diabetic patients suggesting the compensatory mechanism against oxidative stress.

It has been observed over the last few years that oxidative stress in diabetes is responsible for the development of diabetic complications (Mashael et al, 2012).The role of superoxide dismutase (SOD) as an antioxidant enzyme comprises of dismutation of superoxide anion radical at physiological pH. Superoxide dismutase ensures that no superoxide anion is accessible to react with hydrogen peroxide to form the hydroxyl radical through the metal-catalyzed Haber–Weiss reaction. This is suggestive of the fact that increased autoxidative glycosylation of hemoglobin may also have led to increased generation of free radicals like the superoxide anion, thereby causing the depletion of SOD (Hisalkar et al, 2012).The therapy of diabetes with anti-oxidants has been used on diabetic patients during the past decade as a way to compete the oxidative stress.

Material and Methods

The study was conducted on 50 diabetic patients (Type-2), both males (n =28) and females (n=22) between the age group 35-65 years who were registered at the diabetic clinic of Baqui Institute of Diabetology and Endocrinology Karachi, Pakistan.

30 age and sex matched control subjects (12 males and 18 females) were also selected from the general population at random for comparison. Ethical approval was obtained from the institutional ethical review board (IERB) before the commencement of the study. Informed consent of the patients was taken with the help of questionnaire. All patients who were diagnosed diabetes mellitus of type -2 using the ADA criteria of fasting blood glucose (FBG) of >126 mg/dl were included in the study. The patients with any recent critical illness were excluded from the study. The blood samples were collected in tubes with EDTA as anticoagulant and analyzed within 2 hours of venepuncture for Platelet indices and HbA1c. Plasma was also separated and analyzed for other Biochemical parameters. The cell lysates were prepared from the remaining erythrocytes, for the evaluation of SOD level and stored in freezer. The stored plasma and lysates were allowed to attain room temperature before analysis. Fasting blood glucose was estimated by following glucose oxidase method on UV- visible spectrophotometer Jenway 6305.The HbA1c was analyzed by automatic D-10 analyzer. Total Protein were estimated by (TP) BIURET method, Total cholesterol were estimated by enzymatic endpoint method, HDL and LDL were estimated by Precipitant Manual method (Randox kit), triglycerides were estimated by GPO-PAP method.

Platelet indices including Platelet count (PLT), Plateletcrit (PCT), Mean Platelet Volume (MPV), Platelet distribution width (PDW) were analyzed by using hematological analyzer ABX micros 60 fully automated analyzer HORIBA (France). (Catalase) were estimated by MODIFIED AEBI method (Aebi, 1973). The SOD activity was estimated in erythrocytes samples (cell lysate) using the commercially available Randox Kit (RANSOD, Cat. No. SD 125).

Statistics:

Data were statistically analyzed using SPSS (version 20) Software. Independent samples were examined with student's t test. P-values at 95% confidence intervals (CI) were also calculated. P-value of < 0.05 was taken as significant for all comparisons.

Result

Total 50 Diabetic patients (Type-2) (28 male & 22 females) and 30 healthy control (12 male & 18 females) subjects fulfilling the selection criteria were allocated to male and female groups. Mean age of control is 45±3 years and 52±7 years for patients. Blood samples were collected and analyzed for fasting blood glucose, HbA1c, Total Protein ,Lipid Profile (Total Cholesterol, HDL ,LDL and Triglycerides,) Platelet indices (PLT, PCT, PDW, MPV) and Antioxidant enzyme Catalase (CAT) and Superoxide dismutase (SOD) level. The results of biochemical parameters, Platelet indices and antioxidant enzymes (CAT & SOD) status were compared in diabetic patients and control subjects. Significant increase in FBG was found in diabetic patients 164.99±6.22 as compare to control group 88.62±2.01.The level of HbA1c was also greater in diabetic patients 8.28±0.29 as compare to control group 4.62±0.05. The level of FBG and HbA1c were found to be increased in diabetic male and female patients when compared to their respective controls **(Table -I)**. Diabetic patients also revealed significant increase in Total Protein when compare with control group ($P = 0.0001$). Among Lipid profile; Total Cholesterol, LDL and TG were found to be significantly increased ($P= 0.0001$ and $P= 0.0094$ respectively) where as HDL was found to be significantly decreased in diabetic patients as compared with control group ($P= 0.0001$).

In Platelet indices no significant variation was found in PLT and PCT values where as MPV and PDW were found to be significantly increases in diabetic patients as compared to control group ($P = 0.0019$ & $P = 0.0056$ respectively). Among Antioxidant enzymes; Catalase activity was found to be significantly increased in diabetics as compare to control ($P=0.0001$) whereas no significant difference was found in SOD activity in diabetic patients **(Table –II)**.When the comparison was made on the basis of sex both male and female patients showed significant increase in FBG, HbA1c, TP, TC, LDL, TG and significant decrease in HDL when compare to their respective controls. Result showed that levels of MPV, PDW and Catalase were found to be significantly higher in diabetic females as compared to male patients indicating the susceptibility of oxidative stress and vascular complications in female patients.

Table I: Comparison between Control and Diabetic Subjects with respect to the, Fasting Blood Glucose, HbA1c, Lipid profile, Platelet Indices and Antioxidant Enzymes Catalase and SOD Activity.

Parameters	Control (n = 30)	Diabetic Patients (n = 50)	P- Value
FBG (mg/dl)	88.62±2.01	164.99±6.22	0.0001*
HbA1c (%)	4.62±0.05	8.28±0.29	0.0001*
TP (mg/dl)	6.66±0.15	8.63±0.27	0.0001*
T.C (mg/dl)	163.84±4.24	223.36±3.96	0.0001*
HDL (mg/dl)	84.49±5.85	35.70±1.64	0.0001*
LDL (mg/dl)	54.73±5.75	137.24±4.34	0.0001*
TG (mg/dl)	136.13±11.85	189.66±13.83	0.0094*
PLT ($10^3/mm^3$)	223.76±14.61	249.30±10.43	0.1504
PCT (%)	0.19±0.01	0.21±0.01	0.1882
MPV (μm^3)	8.44±0.21	9.22±0.14	0.0019*
PDW (%)	13.69±0.35	14.92±0.26	0.0056*
CAT (U/L)	115.26±9.76	277.89±18.41	0.0001*
SOD (U/ml)	206.69±5.02	215.62±9.30	0.4821

n = no of subjects, values are represented as mean ± SEM (Standard error of mean).* $P < 0.05$ is considered to be statistically Significant.

Table II: Variations of FBG, HbA1c, total Protein, Total Cholesterol, HDL, LDL, TG , Platelet Indices (PLT,PCT,MPV,PDW) and Antioxidant enzymes (CAT and SOD) Status in control and Diabetic subjects on the bases of sex.

Variables	Control (n=30)		Diabetic Patients (n=50)	
	Male (n= 12)	Female (n=18)	Male (n= 28)	Female (n=22)
FBG (mg/dl)	81.96±1.89	93.07±2.66	169.46±8.91*	159.29±8.53*
HbA1c (%)	4.45±0.05	4.73±0.08	8.62±0.40*	7.85±0.42*
TP (g/dl)	6.75±0.31	6.61±0.15	8.37±0.24*	8.95±0.54*
T.C (mg/dl)	171.8±4.31	158.52±6.24	224.72±5.16*	221.63±6.28*
HDL (mg/dl)	80.00±8.41	87.48± 8.08	36.89±2.22*	34.19±2.46*
LDL (mg/dl)	40.72±6.58	64.08±7.90	131.95±6.7*	143.97±4.77*
TG (mg/dl)	159.75±22.18	120.38±12.27	207.63±22.26*	166.78±12.63*
PLT ($10^3/mm^3$)	206.16±25.28	235.5±17.63	246.53±13.8	252.81±16.25*
PCT (%)	0.16±0.01	0.21±0.019	0.20±0.01	0.22±0.01
MPV (μm^3)	8.12±0.25	8.65±0.316	8.95±0.16*	9.57±0.23*
PDW (%)	13.70±0.47	13.68±0.511	14.41±0.27*	15.56±0.46*
CAT (U/L)	110.20±16.56	118.64±12.28	268.48±27.71*	289.87±23.02*
SOD (U/ml)	210.01±8.48	204.48±6.327	212.60±12.13	219.45±14.7

n = no: of subjects, values are represented as mean ± S.E.M (Standard error of mean).* statistically significant as compared to control.

Discussion

The study included 30 control subjects and 50 diabetic patients. In this study Biochemical variation of blood glucose, HbA1c, Total protein, Total Cholesterol, HDL, LDL, TG, Catalase and SOD were determined in control and diabetic subjects. The level of blood glucose, HbA1c, Total Protein, Total cholesterol, TG, LDL were higher in diabetic patient as compare to control subjects (P= 0.0001). Antioxidant enzyme (Catalase) was significantly increased in diabetic subject as compared to control. Changes in blood parameter (PLT, PCT, MPV, and PDW) were also observed. MPV and PDW were found to be increased in diabetic patients as compare to control subjects.

In this study elevated HbA1c level in diabetics shows that higher the blood concentration greater will be chance of glucose molecules that bound to hemoglobin which may affects the proper functioning of hemoglobin and concern with diabetic complications.

The protein level was found to be increased in diabetic patient may it could be happened due to increases in both protein breakdown and protein synthesis during insulin deprivation. Many of the chronic complications of diabetes involve changes in structural proteins. Alterations in protein synthesis and degradation can also adversely affect the repair of tissue after injury or infection (Bennet et al, 1994).

Lipid abnormalities significantly contribute to the increased risk of cardiovascular disease and other morbidity in diabetics. In this study the level of Total Cholesterol, LDL, TG, were increased and HDL level is decreased in diabetics. Higher serum cholesterol in diabetics than controls could be attributed to the acetate metabolism, a precursor of cholesterol, formed in increased amounts from fatty acids catabolism, carbohydrates and amino acids. Individuals with type 2 diabetes have a 2–4-fold increase in their lifetime risk of developing cardiac diseases, which is the leading cause of death among diabetics. This is due to the alteration in lipid metabolism. This study has been suggested that the increase in triglyceride may be due to insulin deficiency which results faulty glucose utilization causes hyperglycemia and mobilization of fatty acids from adipose tissue. The fatty acid from adipose tissue are mobilized for energy purpose and excess fatty acid are stored in liver and converted to triglyceride.

In Present study Correlation analysis revealed that significant correlation existed between biochemical parameters like significant positive correlation was found between FBG and HbA1c (r=0.282*,P = 0.048),HbA1c and HDL (r = 0.369** ,P= 0.008) Total Cholesterol and LDL (r= 0.613**,P=0.000). whereas significant negative correlation existed between HbA1c and Total Protein (r= -0.452**,P=0.000), HDL and Total Cholesterol (r = -0.291* ,P= 0.040), HDL and LDL(r = -0.360* ,P= 0.031), LDL and Triglyceride (r = -0.549**,P= 000) **(Table III)**.

Correlation analysis for Platelet indices revealed that significant positive correlations were found between PLT and PCT (r=0.873**,P = 0.000),MPV and PDW (r = 0.501** ,P= 0.000)**(Table-IV).** As we have prior reported that variation in morphology of platelets and roles are linked with pathological processes and high risk of developing vascular complications in diabetic patients (Jabeen et al, 2013). Outsized platelets are more thrombogenic and thus putting the patient at a privileged risk status. Furthermore increased MPV is linked with greater risk for stroke, myocardial infarction and transient ischemic attacks.

Our Study showed that antioxidant enzyme (Catalase) level is increased in Diabetic subject as compare to Control subjects. Correlation analysis for antioxidant enzymes indicate that significant negative correlation was found between HbA1c and CAT(r= -0.371**, P = 0.008) **(Table –V)**. It is suggested that persistent hyperglycemia causes increased production of free radicals especially reactive oxygen species (ROS). The increase in the level of ROS in diabetes could be due to their increased production and/ or decreased destruction by catalase (CAT). Catalase catalyses the decomposition of hydrogen peroxide (H_2O_2) to water and oxygen. It is also known that in diabetic patients, autoxidation of glucose results in the formation of hydrogen peroxide (H_2O_2) which also enhances inhibition of antioxidant enzymes.

No significant difference was found in SOD activity between diabetic and control groups. Our correlation study showed that significant positive correlation was found between HbA1c and SOD (r= 0.425**,P = 0.002) and negative correlation was found between CAT and SOD (r= - 0.403**,P = 0.004) **(Table –V)**. The effect of diabetes on the status of SOD is contradictory, with no distinguish pattern based on gender or disease duration. Numerous reports regarding the SOD activity in diabetes mellitus are controversial. Some of the studies give you an idea about an increase in the SOD activity which might be, due to compensatory act of enzyme SOD providing resistance to oxidative stress in diabetics (Jabeen et al, 2012) whereas some reports show no change in SOD level (Kesavulu et al, 2000). It is suggested that administration of selective antioxidants along with minerals and essential trace elements might be efficient in minimizing toxic effects produced by oxidative stress (Rains and Jain, 2011).

Table III: Correlations analysis between Biochemical Parameters

		FBG	HBA1c	TP	TC	HDL	LDL	TG
FBG	Pearson Correlation	1	.282*	-.268	-.021	-.038	.144	-.153
	Sig. (2-tailed)		.048	.060	.884	.792	.319	.290
	N	50	50	50	50	50	50	50
HBA1c	Pearson Correlation	.282*	1	-.452**	-.215	.369**	-.188	.115
	Sig. (2-tailed)	.048		.001	.134	.008	.190	.426
	N	50	50	50	50	50	50	50
TP	Pearson Correlation	-.268	-.452**	1	.265	-.188	.001	.072
	Sig. (2-tailed)	.060	.001		.063	.191	.993	.617
	N	50	50	50	50	50	50	50
TC	Pearson Correlation	-.021	-.215	.265	1	-.291*	.613**	-.001
	Sig. (2-tailed)	.884	.134	.063		.040	.000	.995
	N	50	50	50	50	50	50	50
HDL	Pearson Correlation	-.038	.369**	-.188	-.291*	1	-.306*	.098
	Sig. (2-tailed)	.792	.008	.191	.040		.031	.500
	N	50	50	50	50	50	50	50
LDL	Pearson Correlation	.144	-.188	.001	.613**	-.306*	1	-.549**
	Sig. (2-tailed)	.319	.190	.993	.000	.031		.000
	N	50	50	50	50	50	50	50
TG	Pearson Correlation	-.153	.115	.072	-.001	.098	-.549**	1
	Sig. (2-tailed)	.290	.426	.617	.995	.500	.000	
	N	50	50	50	50	50	50	50

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table IV: Correlations analysis of FBG and HbA1c with Platelet Indices

		FBG	HBA1c	PLT	PCT	MPV	PDW
FBG	Pearson Correlation	1	.282*	.042	-.081	-.211	-.082
	Sig. (2-tailed)		.048	.773	.578	.141	.570
	N	50	50	50	50	50	50
HBA1c	Pearson Correlation	.282*	1	.134	.192	-.024	.044
	Sig. (2-tailed)	.048		.353	.183	.866	.760
	N	50	50	50	50	50	50
PLT	Pearson Correlation	.042	.134	1	.873**	-.005	-.032
	Sig. (2-tailed)	.773	.353		.000	.973	.824
	N	50	50	50	50	50	50
PCT	Pearson Correlation	-.081	.192	.873**	1	.265	.004
	Sig. (2-tailed)	.578	.183	.000		.063	.977
	N	50	50	50	50	50	50
MPV	Pearson Correlation	-.211	-.024	-.005	.265	1	.501**
	Sig. (2-tailed)	.141	.866	.973	.063		.000
	N	50	50	50	50	50	50
PDW	Pearson Correlation	-.082	.044	-.032	.004	.501**	1
	Sig. (2-tailed)	.570	.760	.824	.977	.000	
	N	50	50	50	50	50	50

*. Correlation is significant at the 0.05 level (2-tailed).

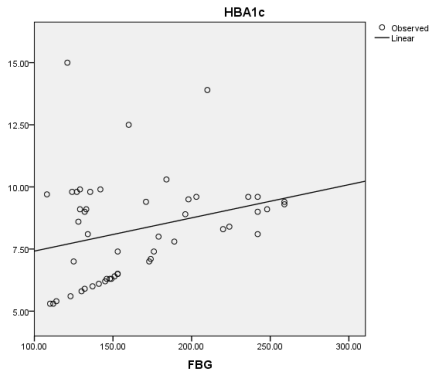
**. Correlation is significant at the 0.01 level (2-tailed).

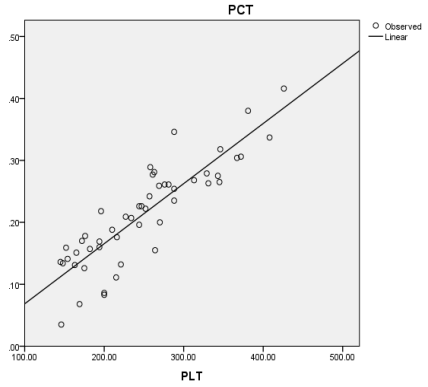
Table V: Correlations analysis of FBG and HbA1c with Antioxidant enzymes Catalase and SOD

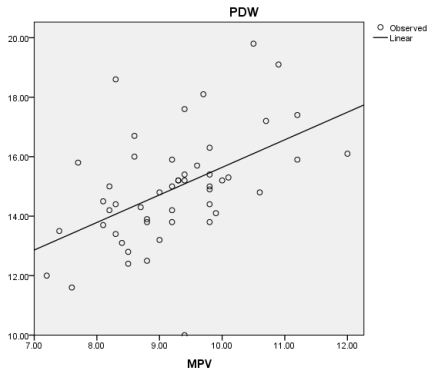
		FBG	HBA1c	CAT	SOD
FBG	Pearson Correlation	1	.282*	.082	-.069
	Sig. (2-tailed)		.048	.573	.635
	N	50	50	50	50
HBA1c	Pearson Correlation	.282*	1	-.371**	.425**
	Sig. (2-tailed)	.048		.008	.002
	N	50	50	50	50
CAT	Pearson Correlation	.082	-.371**	1	-.403**
	Sig. (2-tailed)	.573	.008		.004
	N	50	50	50	50
SOD	Pearson Correlation	-.069	.425**	-.403**	1
	Sig. (2-tailed)	.635	.002	.004	
	N	50	50	50	50

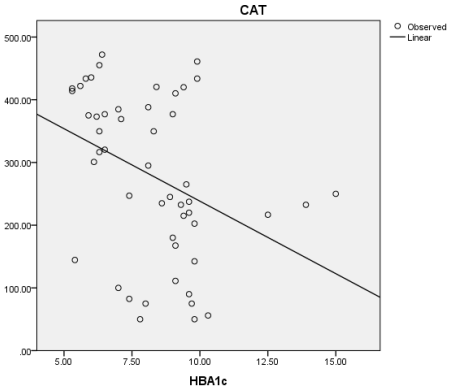
*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).









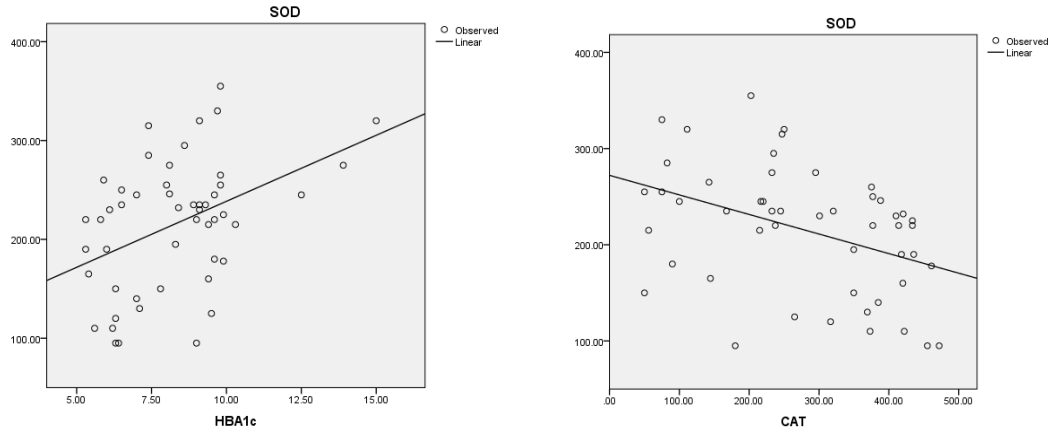


Fig 1: Regression plots showing correlation between FBG with HbA1c (positive correlation), PLT with PCT (Positive correlation), MPV with PDW (Positive correlation), HbA1c with CAT (negative correlation), HbA1c with SOD (Positive correlation), CAT with SOD (negative correlation),

Conclusion

Poor Glycemic control causes alteration in various biochemical parameters as well as hematological indices especially platelet indices. Hyperglycemia induces the production of ROS causing oxidative stress as well as lipid peroxidation which may accelerate vascular complication in diabetics. The study indicate the clinical usefulness of HbA1c level ; platelet indices chiefly MPV and PDW and antioxidant enzymes CAT and SOD level as surrogate markers that may contribute in early finding of micro and macro vascular complications in diabetics. Good glycemic control along with Antioxidant therapy could be supportive and beneficial in reducing harmful effects caused by oxidative stress

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