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LIPID PROFILE IN EXPERIMENTAL DIABETES AS A PROMOTING FACTOR IN THROMBOSIS

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ABSTRACT

Hyperglycemia has a role in development of tissue hypoxia, a reasonable and a significant factor in atherogenesis. The persent study evaluates this diabetic complications through determination of Glycosylated hemoglobin AI (GHb_{A1}), total cholesterol (Tc), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), triglyceride (TG), malondialdehyde in erythrocytes membrane (RBCs MDA), Lipoprotein (a) [Lp(a)], platelet cholesterol/phospholipid ratio (C/P ratio), fibrinogen, antithrombin III (AT III) and plasminogen. Streptozotocin (STZ) diabetic rats were compared with normal rats. STZ induced significant increase in glucose, GHb_{A1}, Tc, LDLc, Lp(a), RBCs MDA, fibrinogen, plasminogen and C/P ratio. On the other hand, it significantly decreased the HDLc and AT III. This study aimed to correlate blood coagulation factors and changes in lipid and lipoproteins in diabetes mellitus.

INTRODUCTION

Certain studies referred to effect of hyperglycemia in development of tissue hypoxia and a significant factor in atherogenesis[1] etiology. Pathogenesis of arterial thrombosis may be related to:

i-Vascular substrates (subendothelium, media or ruptured plaque, prosthetic material or residual thrombus)[2],

ii- Rheology of blood flow (high flow disturbance by stenosis or branching) increased platelet deposition, while stasis favour fibrin formation[3].

iii-Systemic hemostatic thrombotic state (levels of catecholamines and various lipoproteins coagulation and other factors) [4].

These factors are related to the overall thrombogenicity dictate the types and potency of the therapy required[5]. Normal hemostatic process may be modified by diabetes, prothrombotic state[6], platelet hyperactivity[7], activation of the coagulation system and lastly hypofibrinolysis[8].

Atherosclerosis represents a list of arterial changes which occur primarily within intima. This is consisting of local accumulation of blood constituents, fibrous tissue, calcium deposite, lipids in and around cells of intimal space[9]. It is also associated with cellular and fibrous proliferation which leads to narrowing of vascular lumen[10]. This will reduce the blood flow through the involved artery and thereby disturbs the tissue functions[11]. These changes are very marked in diabetes and usually enhanced by multiple mechanisms[12]. Hyperglycemia may injure the endothelial cells initating the atherosclerosis process. **Syeish et al.,**[13] stated that glycosylated hemoglobin has been extensively found in clinical follow up of diabetes. This compound is resulted from nonenzymatic reaction between glucose and terminal amino group of B chain hemoglobin so it is a derivative stable for life span of RBCs[14]. It depends on two factors, life span of RBCs and blood sugar level[15].

Also, hypercholesterolemia is often observed in diabetes. VLDL particles contains about 20% cholesterol, hence any increase in its level may reflect certain degree of hypercholesterolemia[16]. Plasma HDLc was reported to be low in diabetes[17]. Certain studies suggested a close link between the low levels of HDLc and the higher risk of coronary artery disease (CAD) [18]. It has been reported that two types of modified LDLc are present in diabetes glycated LDLc[19] and oxidized one[20]. Hypertriglyceridemia is mostly encountered in diabetes, this is related largely to the degree of diabetic control[21].

Moreover, lipid peroxidation is a complex process usually associated with certain pathologic conditions such as diabetes mellitus[22]. It is a chain of reactions which provides a continuous supply of free radicals that initiate further peroxidation. Lipoprotein (a) has been postulated to bring about correlation between atherosclerosis and thrombosis. It is assumed that Lp (a) might reduce fibrinolytic activity through Lp(a)'s binding to endothelial plasminogen receptors[23]. It may be taken up by macrophages the scavenger receptor pathway, facilitating foam cell formation which is implicated in the formation of atherosclerotic plaques[24].

Hyperglycemia is a causal factor for higher Lp (a) levels[25]. In diabetes platelet function may demonstrate certain abnormalities which have an important role in atheroma development subsequently vascular occlusion. Platelets obtained from diabetic patients have been shown to exhibit increased sensitivity to aggregating agents. Abrams et al., [26] showed enhanced collagen-induced aggregation and thromboxane A2 (TXA2) formation[27]. Fibrinogen is a multifunctional molecule serving not only as a substrate for thrombin in fibrin formation but also as an adhesive molecule for platelet aggregation[28]. Increased fibrinogen has been reported in patient with atherosclerosis[29] in whom they are predictive of cardiovascular events[30]. Certain studies demonstrated low activity of AT III in diabetics, this may promote fibrin clot formation[31].

Plasminogen, the precursor of the main fibrinolytic enzyme plasmin, can bind weakly to

specific sites exposed on the fibrin network[32]. Thus, aim of the present work is to study the interaction and correlation between disturbances in lipid metabolism in diabetes and atherothrombosis.

MATERIAL AND METHODS

Animals and drugs:

Adult male albino rats weighing180±20 g were used in the present work. Rats were kept free on access to standard laboratory chow and tap water *ad libitum* for 10 days before beginning the experimental protocol. Animals were divided into two weight-matched groups; the normal control group and STZ-treated group (for induction of experimental diabetes).

STZ was given by single IP injection at a dose level of 35 mg/kg (body weight) dissolved in citrate buffer at pH 4.5. Three weeks later blood samples were collected and processed for blood glucose determinations. Animals that recorded 200-400 mg/dl were selected for the study. Blood samples were collected from sinus orbitus vein of fasting rats, half of the blood was collected on EDTA and the other on sodium citrat solution (0.11 mol/L) at 1.9 (vol/vol).

1- Citrated blood was used for determination of fibrinogen, antithromobin III, plasminogen and platelet preparation for further analysis[33].
2- Blood collected in EDTA was processed for determination of GHb_{A1}, total cholesterol, LDLc, HDLc, Lp(a) and preparation of red blood cells for further analysis[34].

Methods:

Analytical procedures were used for determination of GHb_{A1}, [35], Tc[36], HDL[37], LDLc [38], TG [39], RBCs MDA[34] C/P ratio[40&41], fibrinogen[42], plasminogen[43]. LP(a) was determined using immunoprecipitin analysis (SPQ antibody reagent set for LP(a)) manufactured by INCSTAR corporation-Stilwater, Minnesota USA. AT III was determined by radio immunodiffusion (RID) method.

Statistical analysis and calculations:

Data of the present study were presented in the form of mean ± S.D. Test on significance was carried out following the unpaired "t-test".

RESULTS

Induction of diabetes in rats significantly increased the blood glucose level, glycosylated hemoglobin and RBCs malondialdehyde[1]. The percentage increases were 275.4%, 123.7% and 104% of control respectively (table 1). There is a positive correlation between the increase in RBCs malondialdehyde levels and glycated hemoglobin ($r = 0.95$ at $P < 0.01$).

Table (1): Effect of STZ on blood glucose, GHb_{A1}, and RBCs MDA of rats.

Parameter	Normal $\bar{X} \pm SD.$	Diabetic $\bar{X} \pm SD.$	% Change from normal rats
Blood glucose mg/dl	107. 83±5. 49	404.83±11.4*	+ 275.4
GHb_{A1} %	6.53±0.26	14.61±0.27*	+ 123.7
RBCs MDA	0.98±0.17	2.0±0.17*	+ 104

* Significantly different from normal at $P < 0.01$.

The total chosterol, LDLc, TG, Lp(a) and C/P ratio levels were significantly increased in STZ diabetic rats (table 2). The percentage increases were 69.9%, 131.13%, 77.8% 104% and 89% respectively whereas, the blood level of HDLc was significantly decreased by 19.5% of control value. There were a postive correlation between changes in blood levels of Lp(a) and both GHb_{A1} and RBCs MDA ($r = 0.73$ and 0.73 at $P < 0.01$ respectively) and a postive correlation between C/P ratio and RBCs Mda ($r = 0.99$ at $P<0.01$).

Table (2): Effect of STZ on Tc, HDLc, LDLc, TG Lp(a) and C/P ratio of rats.

Parameter	Normal $\bar{X} \pm SD.$	Diabetic $\bar{X} \pm SD.$	% Change from normal rats
Tc mg/dl	77.5±3.27	131.66±5.2*	+ 69.9
HDLc mg/dl	25.66±1.03	20.66±1.03*	- 19.5
LDLc mg/dl	35.33±1.21	81.66±4.71*	+ 131.13
TG mg/dl	82.5±10.36	146.66±7.11*	+ 77.8
Lp(a) mg/dl	12.9±1.18	24.4±2.58*	+ 89
C/P ratio	0.45±0.016	0.708±0.05*	+ 57.3

* Significantly different from normal at $P < 0.01$.

Results in table (3) showed that there were a significant increase in the blood levels of fibrinogen and plasminogen recording 168%, 40.4% increase compared with normal rats. On the other hand AT III blood level was significantly decreased recording 57.2% from control value. There were positive correlation between the blood levels of fibrinogen and C/P ratio (Fig. 1), RBCs MDA (Fig. 2) and Lp (a) (Fig.3).

Table (3): Effect of STZ on Fibrinogen, AT III and plasminogen of rats.

Parameter	Normal $\bar{X} \pm SD.$	Diabetic $\bar{X} \pm SD.$	% Change from normal rats
Fibrinogen mg/dl	197±19	528±52*	+ 168
AT III mg/dl	30.75±1.98	13.15±1.62*	-57.2
%	119.16±11.37	167.33±14.47*	+ 40.4

* Significantly different from normal at $P < 0.01$.

Moreover, there were positive correlations between plasminogen blood level and RBCs MDA (Fig. 5) and Lp(a) (Fig. 6). However, there was a negative correlation between the blood level of AT III and RBCs MDA (Fig. 4).

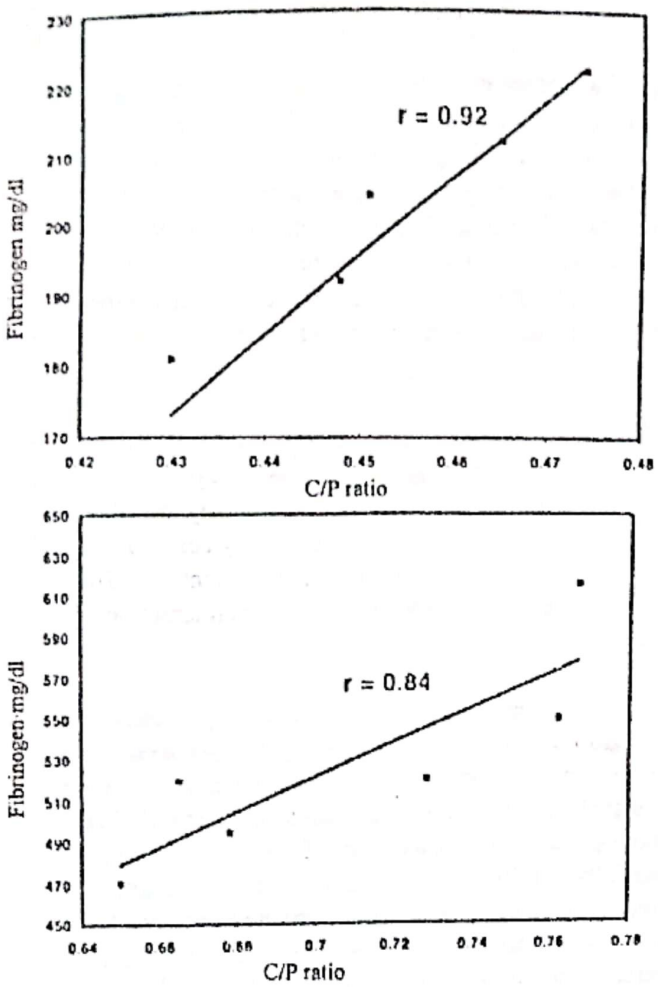

Fig. (1): Correlation between Platelet Cholesterol/Phospholipid ratio and fibrinogen in normal and diabetic rats.

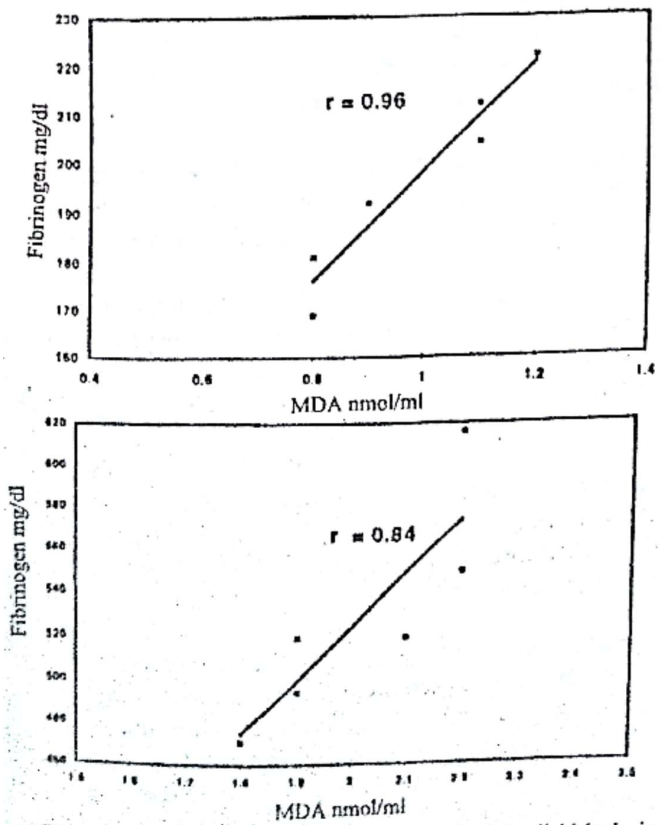

Fig. (2): Correlation between fibrinogen and Malondialdehyde in normal and diabetic rats.

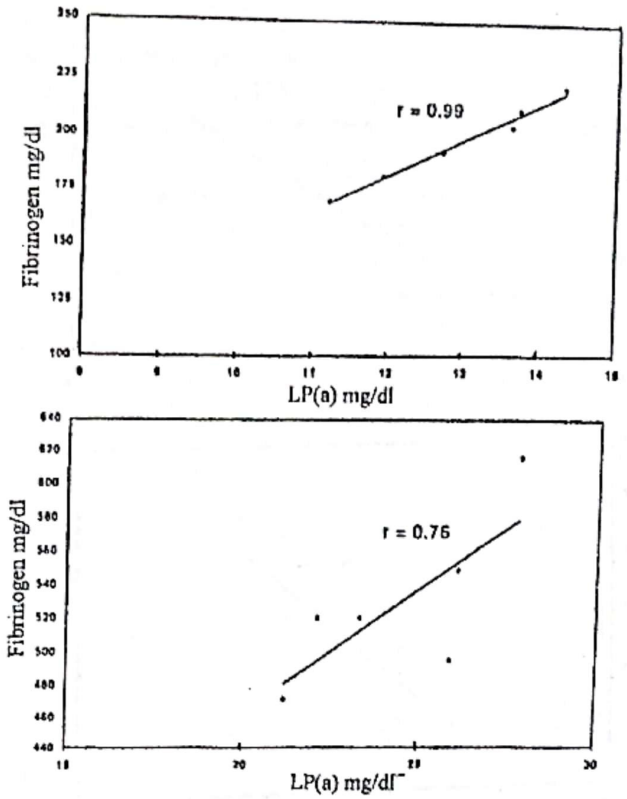

Fig. (3): Correlation between fibrinogen and Lipoprotein (a) in normal and diabetic rats.

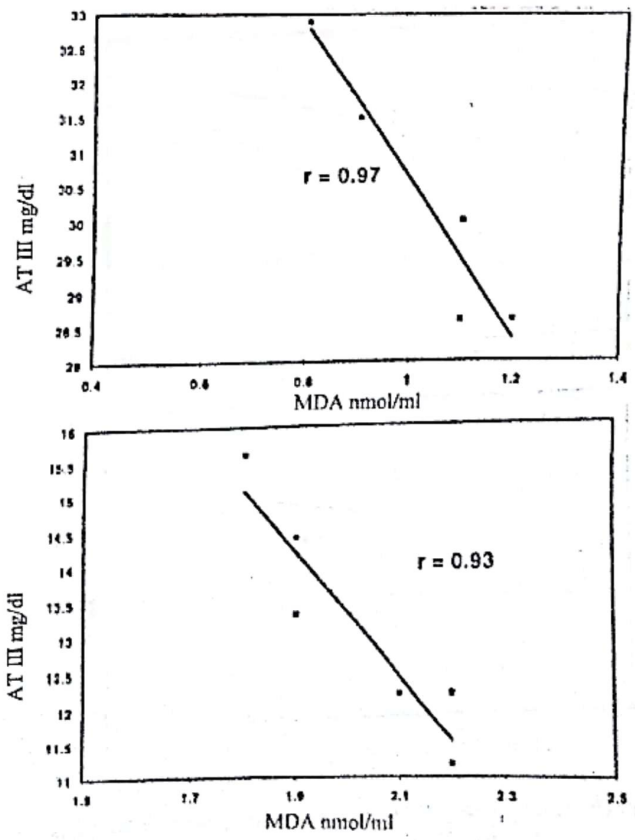

Fig. (4): Correlation between antithrombin III and Malondialdehyde in normal and diabetic rats.

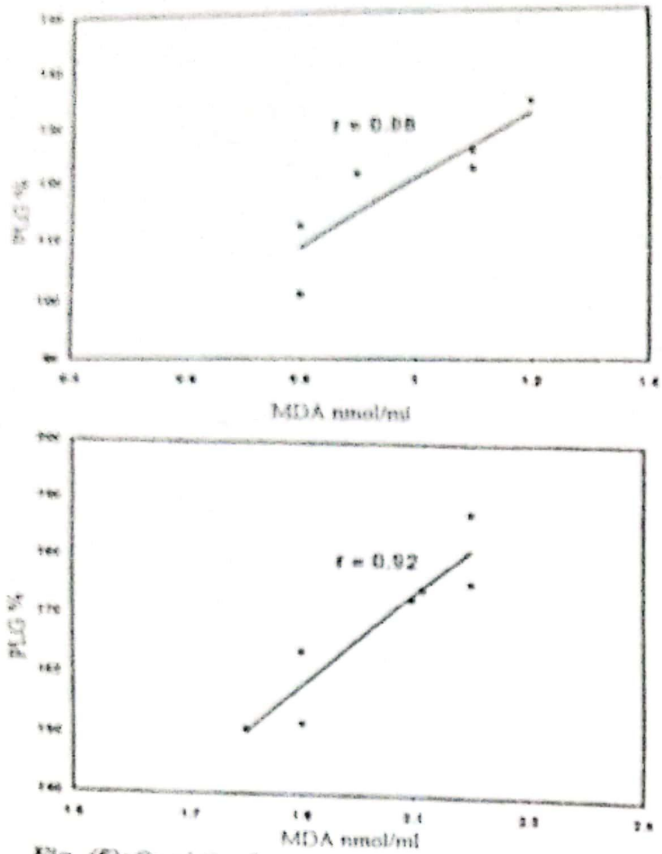

Fig. (5): Correlation between Plasminogen and Malondialdehyde in normal and diabetic rats

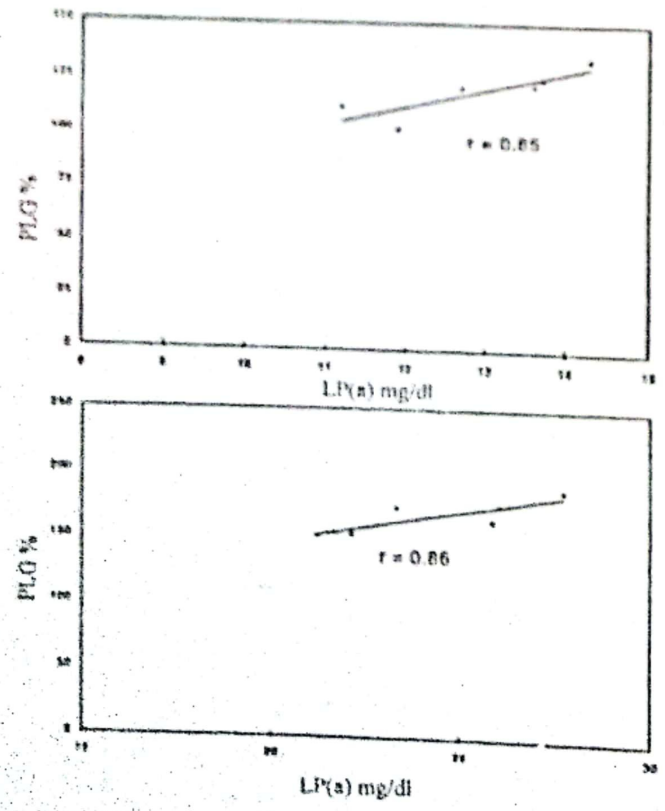

Fig. (6): Correlation between Plasminogen and Lipoprotein (a) in normal and diabetic rats.

DISCUSSION

The present work was directed to study the multiple interactions between diabetes mellitus and pathophysiological process leading to microvascular diseases. The main pathogenic pathway of atherothrombosis and their relation to diabetes are largely and frequently analyzed. In this work we focused on some particular aspects of this process namely, impairment of fibrinolysis and lipid metabolic disturbances.

Results of the present study revealed that STZ induced significant hyperglycemia in approval with other studies[45]. Such hyperglycemia may be due to certain dysfunctions of insulin secretory cells (B-cells) [46]. This is attributed to enhancement of H_2O_2 generation by STZ inducing DNA fragmentation and lastly B-cells destruction[47].

Subsequently STZ significantly increased hemoglobin glycosylation. this is approved with hyprglycemic state[48]. Additionally certain abnormalities may be also expected where different proteins are subjected to further glycosylation especially LDL[49]. In turn platelet uptake of glycosylated LDL may be activated followed by increased tendency to aggregation, finally induced an alteration in platelet membrane structure[50]. Increased glycosylation of membrane proteins may be associated also with reduced membrane fluidity[51]. So glycosylate plasminogen appears to be less transformable to the active form (plasmin) relative to the native one [35]. Also fibrin derived from glycosylated fibrinogen appears to be resistance to fibrinolysis[52].

In addition, glycosylated end product of proteins have been found largely within atherosclerotic plaque of diabetic individuals[53]. Present results showed that STZ diabetic rats exhibited a significant increase in total cholesterol, LDLc and triglycerides but HDLc showed a significant decrease[54]. Lipoprotein abnormalities are commonly observed in diabetics and contributing largely to atherogenesis development[55]. Marked hypertriglyceridemia may be due to defective removal of triglyceride rich lipoprotein from circulation by lipoprotein lipase[56]. Lipolysis enhancement of triglyceride rich lipoprotein may lead to an increase in HDLc. Therefore a precursor product relationship exists between the two[57].

Human and experimental studies demonstrated higher level of lipid peroxidation products in diabetics which correlated with GHb_{A1} level. In vitro studies showed that glucose can enolize and thereby. reduce molecular oxygen under physiological conditions yielding α-keto aldehydes, hydrogen peroxide and free radical intermediates[58].

Oxygen free radicals formed in surplus of erythrocytes detoxifying capacity may lead to vascular complications in diabetes through decreased level of certain antioxidants such as vitamin E, superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and ascorbic acid[59]. From the complications derived from lipid peroxidation is the disturbance in NO/O_2 in humans with diabetes mellitus and hyperlipidemia[60]. Dysfunction of the NO/O_2 system may be a common mechanism by which such apparently diverse conditions lead to chronic vascular complications. Present study demonstrated higher Lp(a) level of diabetic rats positively correlated with GHb_{A1} level. The mechanism by which plasma Lp(a) level increase in diabetic may result from increased synthesis and/or decreased catabolism. Lp(a) is considered to be an independent risk factors for premature atherosclerosis[24]. Recently, it has been shown that Lp(a) can induce free radical generation[61] which may play a role in defective vascular relaxation of atherosclerotic arteries[62]. Other possible mechanism of Lp(a) as a risk factor, is its structural {[apo(a)] homology with plasminogen. **Edelberg et al.**[63] suggested that it may act as competitive inhibitor to plasminogen. Present study demonstrated a positive correlation between Lp(a) and plasminogen (Fig.10). Finally treatment directed to decrease Lp(a) level may be requested for diabetics suffering from coronary artery disease[64].

Present work also showed that STZ induced an increase in platelet cholesterol/phospholipid molar ratio (C/P ratio). Alteration of platelet function in diabetics may be translated to an increase in platelet adhesiveness and tendency to aggregation[41]. Changes in C/P ratio may be attributed to hypercholestrolemia observed in STZ rats. Hypercholesterolemia may enhance the release of certain platelet parameters like histamine and adenosin diphosphate[65]. These parameters activate phospholipase A2 which induces release of arachidonic acid from phospholipids[66].

Conversion of prostaglandin G_2 to prostaglandin H_2 during their biosynthesis from arachidonic acid may produce oxygen free radicals[67]. The latter exerts certain cytotoxic effects through enhancement of membrane phospholipids peroxidations. This may lead to certain changes in membrane fluidity, permeability and finally loss of integrity[68]. Activated platelets accumulated at vascular injury sites (due to hyperglycemia) may acquire certain alterations in their cell membranes. This represents the primary source of phospholipid surface upon which the coagulation cascade[69]. C/P ratio showed positive correlation with fibrinogen and MDA (Fig.2).

Fluid phase studies of coagulation process revealed that diabetes is usually associated with hypercoagulable state[70]. Diabetic rats showed significant increase in fibrinogen, plasminogen joined with a decrease in AT III level. A direct link between abnormal glucose levels and increase activity of coagulation system has been demonstrated[71]. Direct correlation between the simultaneous increase of some coagulation parameters and certain markers of oxidative stress in diabetes have been recently reported[72]. In addition, the hyperglycemia-induced thrombin activation may be prevented by antioxidant such as glutathione[73]. **Ceriello et al.**[73] referred to certain hypothesis where hyperglycemia can induce tissue factor[74] and rapidly decrease nitric oxide (NO) production in endothelial cells[75]. The first one is a potent procoagulant factor[76&79] and the second operates as platelets antiaggregatory[77]. Glycosylated plasminogen appears to be less transformable to the active form (plasmin) relative to the native one. Also fibrin derived from glycosylated fibrinogen appears to be resistant to fibrinolysis.

We can conclude that lipimic and thrombotic risk factors are commonly observed to certain extent in diabetes . In support to our findings, **Heinrich et al.**[78], demonstrated a strong relation between LDLc levels and coronary heart disease associated with higher level of fibrinogen. Also, it has been referred to plasma fibrinogen and Lp(a) to myocardial infarction risk factors as they have some similarity to HDL and LDL cholesterol behaviour.

Finally, levels of plasma lipids and thrombotic factors should be evaluted to assess clinical cardiac events[80] combination of lipid profile and other thrombogenic factors in association with family history study of diabetics may lead to proper treatmet of such disturbance.

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دراسة التغيرات الناشئة فى الدهون ومشتقاتها فى مرض البول السكرى وتأثيرها على عوامل التجلط

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تعد هذه الدراسة محاولة لإلقاء الضوء على علاقة بعض عوامل التجلط وكذا التغيرات فى الدهون ومشتقاتها ومدى تأثير كل منهما على الآخر فى مرض السكر التجريبى.

وقد تم تقدير كل من الليبوبروتين (أ) والفيبرينوجين الانتيثرومبين الثلاثى والبلازمينوجين والكولسيتيرول الكلى ومشتقاته (عالى ومنخفض الكثافة) والتراى جليسيريدات فى البلازما وكذا الليبيدات فوق المؤكسدة فى جدار كرات الدم الحمراء ونسبة الهيموجلوبين المتسكر فى الدم ونسبة الكلوليسترول إلى الفوسفوليبيدات فى جدار الصفائح الدموية للجرذان المصابة بالسكرى والمحدث بحقن الاستربتوزوتوسين.

أدى هذا العقار إلى زيادة جوهرية فى الجلوكوز والفيبرينوجين والليبوبروتين (أ) والكوليسترول عالى ومنخفض الكثافة والجلسريدات الثلاثية وإلى انخفاض معنوى فى كل من الانتيثرومبين الثلاثى وكوليسترول الليبوبروتينات عالية الكثافة فى البلازما بينما زادت نسبة الليبيدات فوق المؤكسدة فى جدار كرات الدم الحمراء ونسبة الكوليسترول إلى الفوسفوليبيدات فى جدار الصفائح الدموية والهيجوجلوبين المتسكر وذلك بالمقارنة بالجرذان الطبيعية.

هذه الدراسة تبين أن الإختلال الناجم فى عوامل التجلط وكذا دهون الدم هو أحد المضاعفات المترتبة على مرض السكر وخاصة فى الذين لا يخضعون لبرنامج علاج متكامل ومستمر.