DISCUSSION

Diabetes mellitus is defined as the dysregulation of glucose metabolism characterized by chronic hyperglycemia resulting from defects in insulin secretion, decreased insulin sensitivity or a combination of both **(Jachen and Werner, 2006).**

Diabetes leads to a hypercoagulable state. It is associated with the increased production of tissue factor by endothelial cells and VSMC, as well as increased plasma concentrations of factor VII. Hyperglycemia is also associated with a decreased concentration of antithrombin and protein C, impaired fibrinolytic function, and excess production of PAI-1 **(Beckman et al., 2004).**

The fibrinolytic system is primarily an interaction between plasminogen activators and inhibitors and one response to vascular injury is an activation of t-PA. Increased t-PA activity may therefore be a potential indicator of an early ongoing vascular damage **(David et al., 2009).**

Tissue plasminogen activator level elevates in the plasma of the diabetic patients with lower extremity arterial disease (LEAD) and can be used as an early marker for diagnosis of these cases **(Raffetto et al., 2005)**.

Peripheral arterial disease is a major risk factor for lower-extremity amputation, especially in patients with diabetes. Moreover, even for the asymptomatic patient, PAD is a marker for systemic vascular disease **(Nathaniel, 2003).**

Diabetes mellitus increases the risk for PAD via deleterious effects on the vessel wall e.g., (derangement of nitric oxide

bioavailability in endothelial cell) as well as effects on blood cells e.g., (enhanced platelet aggregation and hypercoagulable state) and rheology e.g., (increased blood viscosity and fibrinogen levels) **(American Diabetes Association, 2003).**

Tissue plasminogen activator (t-PA) is synthesized and released by vascular endothelial cells into the circulating blood as the single-chain form and is the predominant activator in plasma. The main function of t-PA is in the dissolution of fibrin in the vasculature, helping to maintain vessel patency. Tissue plasminogen activator (t-PA) acts by forming a ternary complex with fibrin and plasminogen and catalyzes the conversion of inactive plasminogen to plasmin **(Suzanne et al., 2006).**

Increased t-PA occurs in association with endothelial cell dysfunction and damage; elevated levels may reflect the presence of underlying endothelial damage **(Steins et al., 2000).**

The objective of present study was to evaluate the plasma level of tissue plasminogen activator (t-PA) as an early predictor marker of asymptomatic lower extremity arterial disease (LEAD) in patients with diabetes mellitus. This study was carried out on 80 subjects classified into 3 groups: Group I: - The control group included 20 apparently healthy subjects, Group II: - included 30 insulin -dependent diabetic patients, who were sub-classified into NON LEAD and LEAD and Group III: - included 30 non- insulin –dependent diabetic patients, who were sub-classified into NON-LEAD and LEAD.

In this study BMI was highly significantly increased in group III compared to group I and group II separately while no statistical significant difference was found between group II and group I. These results coincide with the results reported by **Andreas et al.(2002)** who

found a significant increase in BMI in diabetic patients compared to control group, furthermore the results of the study reported by **Ali et al.(1995)** are also in agreement with our results. On the other hand **Morishita et al.(1996)** found no statistical significant difference in BMI between control group and diabetic patients.

The results of the present study revealed that there was no statistical significant difference as regard diastolic blood pressure among all groups. These results coincide with the results in the study reported by **Ali et al.(1995)** who found no statistical significant difference in DBP between control group and diabetic patients. SBP was statistically significantly increased in group II and group III compared to group I with no statistical significant difference found between group II and group III. On the contrary, the study done by **Ali et al.(1995)** reported no statistical significant difference in SBP between control group and diabetic patients.

Moreover, Ankle Brachial Index (ABI) was statistically significant lower in group II and group III compared to group I with no statistical significant difference found between group II and group III. These results coincide with the results reported by **Premanath and Raghunath, (2008)** who found significant decrease in ABI in diabetic patients with and without PAD compared to control group.

In the present study HbA1c was statistically significantly higher in group II and group III compared to group I with no statistical significant difference found between group II and group III. These results coincide with the results of study reported by **Elizabeth et al.(2006)** who found significant increase in levels of HbA1c in type II DM with PAD compared to control group due to chronic elevation of the blood glucose

level.

These results suggested that these patients with diabetes were exposed to hyperglycemia over long periods, with increased and accelerated glycosylation of hemoglobin A within the red blood cell throughout its 120 days life span in the circulation.

The results of the present study, revealed that t-PA was statistically significant higher in group II compared to group I but statistically significant lower in group III compared to group I and group II. These results coincide with the results reported by **David et al.(2009)** who showed that type II diabetes had significantly lower levels of t-PA and type I diabetes had statistically significant higher levels of t-PA than non diabetic subjects. These results are explained by detection of elevated levels fibrinolytic inhibitors, PAI-1 which is generated from fat-laden insulin-resistant adipocyte and lead to suppression of the fibrinolysis in diabetic patients due to negative feed back on tissue plasminogen activator (t-PA) **(Lange et al., 2003).**

In accordance with our results, **Bastard et al.(2000)** reported that increased PAI-1 secretion due to interaction of a number of metabolic and inflammatory factors in type II diabetes can lead to decrease secretion of the tissue plasminogen activator (t-PA).

Our results are also in agreement with that reported by **Stegenga et al. (2006)** who found that t-PA was statistically significant lower in type II diabetes because fluctuating hyperglycemia leads to protein glycation that induce the oxidative stress, endothelial cell dysfunction, extracellular matrix formation and apoptosis. This leads to vascular damage that increases thrombotic formation, stimulates the fibrinolytic system, increases (PAI-1) and decreases t-PA in the late stages.

Our study revealed a statistical significant increase of fibrinogen in group II and group III compared to group I with no statistical significant difference found between group II and group III. These results coincide with the results reported by **Andreas et al.(2002**) who reported that fibrinogen levels in diabetic patients was higher than those in the control group due to increased synthesis and turnover of fibrinogen in diabetics that is related to insulin deficiency. These results were explained by **Meigs et al. (2000)** who suggested that in diabetic patients complicated with vascular disease, there are multiple vascular damages which are responsible for the high fibrinogen level. On the other hand, the study performed by **Pandolfi et al. (2001) revealed that** no statistical significant difference was found in fibrinogen level between control group and diabetic patients.

In the present study there was a statistical significant increase of CRP in group II and group III. These results were in agreement with the results of the study done by **Andreas et al. (2002)** who reported that CRP levels in diabetic patients were higher than those in the control non-diabetic group, suggesting that the hyperglycemia as stress factor affects the CRP levels. The study of **Ridker et al. (2000)** found that in prolonged exposure to hyperglycemia there is an inflammatory process which leads to elevation of CRP level that leads to vascular damage. This stimulates endothelial production of procoagulant tissue factor, leukocyte adhesion molecules, and chemotactic substances and inhibits endothelial cells nitric oxide (NO) synthase, resulting in increased local production of compounds impairing fibrinolysis, such as plasminogen activator inhibitor (PAI-I) which inhibits the secretion of tissue plasminogen activator.

The results of this study also revealed that there was no statistical significant difference between NON LEAD and LEAD in group II as regards t-PA. These results coincide with the results reported by **David et al. (2009)** who found that t-PA was not significantly different in type I diabetes with LEAD compared to NON LEAD.

There was a statistical significant difference between NON LEAD and LEAD in group II in the levels of HDL- C and triglyceride. These results are on the contrary to what was gained from the study done by **Tzoulaki et al. (2006)** who found that there were no statistical significant differences in HDL and triglyceride in type I diabetes with or without PAD.

Otherwise, cholesterol was statistically significantly increased in group II LEAD compared to NON LEAD. These results are on the contrary to what was gained from the study done by **Tzoulaki et al. (2006)** who found that there was no statistical significant difference in cholesterol in type I diabetes with or without PAD.

Moreover, our study showed that there was a statistical significant decrease in ankle brachial index in LEAD compared to NON LEAD in group II.These results coincide with the result showed by **Premanath and Raghunath, (2008)** who found significant decrease in ABI in diabetic patients with PAD compared to diabetic patients without PAD.

On the other hand, there was no significant difference in body mass index, systolic blood pressure, diastolic blood pressure, glycosylated hemoglobin, fasting serum glucose, post prandial serum glucose and diabetic duration between LEAD and NIN LEAD in group II.

In the group III, t-PA was statistically significantly increased in LEAD compared to NON LEAD. These results coincide with the results reported by **David et al. (2009)** who found that t-PA was significantly elevated in type II diabetes with LEAD than NON LEAD.

These results were explained by **Kooistra et al. (1994)** who reported that peripheral ischemia stimulates the compensatory mechanism to sustain circulation in vessels in the early stage of the disease and during this stage the endothelium still contact. It is the major source for secretion of t-PA so, it increases after vascular insufficiency caused by peripheral vascular disease in type II diabetes.

There was no statistical significant difference between NON LEAD and LEAD in group III as regards HDL-cholesterol. These results coincide with the results reported by **Tzoulaki et al. (2006)** who found that HDL-cholesterol wasn`t statistically significantly different in type II diabetes with or without PAD.

Moreover, there was a statistical significant decrease in ankle brachial index in LEAD compared to NON LEAD in the group III. These results coincide with the results showed by **Premanath and Raghunath (2008)** who found significant decrease of ABI in diabetic patients with PAD when compared to diabetic patients without PAD. This study found that atherosclerosis stimulates the formation of atheromatic plaque which affects the blood flow in the blood vessels stimultaneously the change in the endothelial wall of the blood vessels which lost its elasticity and thickened leading to decrease the sound wave that is transmitted through it as it become more flattened and rounded and lead to decrease the ankle systolic pressure.

Otherwise, there was a significant increase in glycosylated

hemoglobin in LEAD compared to NON LEAD in the group III. These results coincide with the results of study reported by **Elizabeth et al. (2006)** who found significant increase in levels of HbA1c in type II DM with PAD compared to type II DM without PAD suggested that these patients with uncontrolled diabetes were exposed to hyperglycemia over long periods, with increased and accelerated glycosylation of hemoglobin A within the red blood cell throughout its 120 days life span in the circulation.

On the other hand, there were no statistical significant difference in body mass index, diastolic blood pressure, fasting serum sugar level, post prandial serum sugar level and diabetics duration between LEAD and NON LEAD of group III.

In the present study, tissue plasminogen activator was positively correlated in group II with duration of diabetes.

Furthermore, in our study tissue plasminogen activator was positively correlated in group III with duration of diabetes and with HbA1c in (total).

In our study, there was no correlation between t-PA and body mass index in group II and group III, while another study done by **Ali Keskin et al. (1995)** showed positive correlation of t-PA with BMI, This observation further supports documented decreased fibrinolytic activity in obesity. These results were explained as an elevation in BMI predisposes to insulin resistance and hyperinsulinism rather than to insulin deficiency.

In our study we found a statistical significant correlation between tissue plasminogen activator and glycosylated hemoglobin in group III

(total).

These results were in agreement with the results shown by **Thomas et al., (2009)**. On the other hand the study reported by **Ali Keskin Et Al., (1995)** found no correlation between t-PA and HbA1c and this was against our study.

So, the concentration of tissue plasminogen activator according to our study seems to be dependent on diabetic control.

Otherwise, our study in groups II and III found no correlation among t-PA and glycosylated hemoglobin, systolic blood pressure, diastolic blood pressure, fibrinogen, C-reactive protein, ankle brachial index, fasting serum sugar, post prandial serum sugar, HDL-cholesterol, LDL- cholesterol, cholesterol and triglyceride.