PyrexJournals

Pyrex Journal of Clinical Pathology and Forensic Medicine
Vol 1 (2) pp. 017-024 November, 2015
http://www.pyrexjournals.org/pjcpfm

Original Research Article

Coagulation State in Diabetic Retinopathy in Type 2 Diabetic Sudanese Patients

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Accepted 11th November, 2015

Diabetes mellitus affects most organs in the body. The manifestations of these effects are generally detected by changes in their functions. Retinopathy generally occurs early in the course of diabetes and, even though no other symptoms are present. It may progress to threaten vision. Therefore, because of potential sequelae to visual function that are preventable, early detection of diabetic retinopathy with an assessment of its severity is needed to prevent loss of vision. The aim of this study is to investigate whether diabetic retinopathy, already associated with microvascular alteration, ischaemia and endothelial dysfunction was also characterized by an abnormal coagulation profile.

Methods: this is a Case-control study in which forty Sudanese type 2 diabetic patients with different degrees of diabetic retinopathy and ten healthy control subjects were included in this study. In all patients, retinopathy was detected by direct opthalmoscopic examination and by using slit lamp biomicroscopy. In both patients and the control group prothrombin time (PT), activated partial thromboplastin time (APTT) and factor VII coagulant activity (VII:c) were done.

Results: Factor VII: c levels were higher in diabetic patients than the control group (p=0.03). There was a significant correlation between factor VII: c level and diabetic retinopathy (p=0.019). Factor VII: c was higher in diabetic patients with retinopathy especially in patients with proliferative retinopathy. PT mean values in diabetic patients were shorter than in the control group (p<0.01). There was a highly significant correlation between PT and diabetic retinopathy (p =0.002). There was no significant correlation between APTT and diabetic retinopathy (p=0.98).

Conclusions: These findings pointed out the presence of a hypercoagulable state in patients with type 2 diabetes with diabetic retinopathy demonstrated by increased factor VII: c level and short PT.

Key words: Diabetes, ischaemia, retinopathy, coagulation.

INTRODUCTION

Diabetes mellitus is a syndrome characterized by chronic hyperglycaemia, disturbed carbohydrate, fat, protein, water, electrolytes and acid base metabolism. It is actually a group of metabolic diseases resulting from defects in insulin secretion, insulin action or both. [1] When viewed in the context of coexisting insulin resistance; lack of insulin effect plays a primary role in the metabolic derangements linked to diabetes and hyperglycaemia in turn plays an important role in disease-related complications. Diabetes affects more than 135 million people. This figure is projected to reach 300 million cases by 2025. Unfortunately rate growth of diabetes is largest in developing nations, where barriers exist to proper diagnosis and treatment. [2] Diabetes is a leading cause of both mortality and early disability. It is a leading cause of end stage renal disease, of blindness and of non-traumatic limp amputations. Diabetes increases the risk of cardiac, cerebral and peripheral vascular disease two – to seven – fold and in the obstetric setting is a major contributor to neonatal morbidity and mortality. [2]

Diabetes mellitus is classified into two broad categories; type I insulin dependent diabetes mellitus (IDDM) and type II non-insulin dependent diabetes mellitus (NIDDM). The categories of type I and type II were retained with the adoption of Arabic numerals instead of Roman numerals. [3] Therefore the ADA /World Health Organization (WHO) recommended the following categories of diabetes:

Type 1 diabetes mellitus: Formerly known as insulin dependent diabetes mellitus (IDDM) or juvenile onset diabetes

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primarily caused by autoimmune pancreatic B cell destruction and characterized by absolute insulin deficiency.

Prevalence/Epidemiology: Type 1 is predominantly a disease of whites and of populations with substantial white genetic admixture, including African American. It is rare in Asian races, Native American and black Africans. Prevalence rates for type I diabetes are relatively accurate, since these patients invariably become symptomatic. Symptoms appear when 80 – 85% of cells are lost. It presents most commonly in childhood with a peak incidence at 9 – 14 years of age, but can be present at any age. It accounts for 10 – 20% of all diabetic patients. More than 90 % of type 1 diabetic patients carry HLA DR3 and /or DR4, compared with 35% of the general population. The relative risk conferred by DR3 is about 7 and by DR4 about 9 but DR3/ DR4 heterozygotes have a relative risk of 14. [4]

Type 2 diabetes mellitus: formerly known as non- insulin dependent diabetes (NIDDM) or adult onset diabetes may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance.

Prevalence /Epidemiology: It is the most common of the hyperglycaemic states. The disease exists in all populations, but prevalence varies greatly; the highest rates ever reported were 34% in the Micronesians of Nauru and 40% in Pima Indians of Arizona. It is most common between forty and eighty years. It is very occasionally seen in young individuals. High prevalence is seen in populations who have changed from traditional to modern life; a phenomenon which is called urbanization. [5] The disease may be present in the sub clinical form for years before diagnosis and the incidence increases markedly with age, the degree of obesity, refined carbohydrates with high energy food and low birth weight. [2]

Other specific types as: Genetic defects of β cell function, genetic defects in insulin action, disease of the exocrine pancreas, endocrinopathies, drug or chemical, gestational diabetes mellitus.

Complications of Diabetes Mellitus

- **Acute Metabolic Complications**

Since the availability of insulin and antibiotics, the number of deaths from acute metabolic complications has decreased [6] acute metabolic complications include the following:

1. Hyperglycaemic States

Metabolic decompensation in diabetes is generally classified into two broad clinical syndromes:

a) Diabetic ketoacidosis

May herald the onset of type 1 diabetes, but most often occurs in established diabetic patients. It may occur at any time during the course of the disease, either because of withdrawal of adequate insulin therapy because of intercurrent stress. Other common precipitations include myocardial infarction, cerebro vascular accident and alcohol intoxication or abuse. [7]

b) Hyperosmolar hyperglycaemic state (HHS)

The metabolic state formerly known as the hyperosmolar non-ketotic state/ coma has been renamed the hyperosmolar hyper glycaemic state. The hallmarks of HHS are severe hyper-osmolarity >320 mosm/l and hyperglycaemia > 600 mg/dl. [2]

2. Hypoglycaemia

Hypoglycaemia occurs often in diabetic patients treated with insulin, but relatively infrequently in those taking a sulphonylurea drug. The risk of hypoglycaemia is the most important single factor limiting the attainment of the therapeutic goal, namely near normal glycaemia. [8]

- **Long-Term Complications of Diabetes Mellitus:-**

Traditionally retinopathy, neuropathy and nephropathy have been designated microvascular complications, which are specific to diabetes, whereas atherosclerosis and its sequel (stroke, myocardial infarction, gangrene) are termed macrovascular complications. Both types of vascular disease cause substantial morbidity and disability.

a. Macrovascular complications:-

Patients with diabetes have an increased prevalence of premature atherosclerotic vascular disease resulting in increased risk of myocardial infarction, stroke and lower extremity gangrene. It accounts for about 70% of deaths. The pathological changes associated with atherosclerosis in diabetic patients are similar to those seen in the non-diabetic population, but they occur earlier in life and are more extensive and severe. [8] The alterations in plasma coagulation proteins have been incriminated as a possible cause. [9]

b. Microvascular complications:-

The effects of microvascular disease are most profound in the retina, kidneys and peripheral nerves. Several biochemical pathways have been proposed to link hyperglycaemia and microvascular complications. These include formation of advanced glycation end products (AGEs), polyol accumulation, oxidative stress and activation of protein kinase C (PKC). These processes are thought to modulate the disease process through effects on cellular metabolism, signaling and growth factors. [10]

Diabetic Nephropathy

Nephropathy is the specific diabetes complications associated with the greatest mortality. Although the vast majority of diabetic patients have some degree of retinopathy, nephropathy develops in only 35 to 45 percent of patients with type 1 diabetes and less than 20 percent of those with type 2 diabetes. The natural history of clinically detectable diabetic nephropathy begins with the development of microalbuminuria (30 to 300mg of albumin per 24 hours). When overt proteinuria (> 500 mg of protein per liter, equivalent to >300 mg of albumin per 24 hours) develops in patients destined to have end –stage renal disease. Unlike the prevalence of retinopathy, the prevalence of nephropathy does not rise continuously with the increasing duration of diabetes. [11]

Diabetic Neuropathy

The clinical manifestations of neuropathy in patients with type 1 or 2 diabetes are protean. A peripheral, symmetric sensorimotor neuropathy is the most common form of diabetic neuropathy, whose other forms include cranial and peripheral motor neuropathies and autonomic neuropathy. Although neuropathy is also more common with a longer duration of diabetes, a relatively severe, early-onset polyneuropathy has been described. [12] Autonomic neuropathy can affect gastric or intestinal motility, erectile function, bladder function, cardiac function, and vascular tone. Gastroparesis may not only cause symptoms, but also alter the absorption of meals and make glycaemic control problematic. Diabetic diarrhea and incontinence are rare, but can be disabling. Impotence is the most common clinical manifestation of autonomic neuropathy, affecting more than 50 percent of men with diabetes. Cardiac autonomic neuropathy may result in resting tachycardia and postural hypotension. [13]

Diabetic Retinopathy (DR)

DR refers to progressive pathologic alterations in the retinal microvasculature leading to areas of retinal non perfusion, increased vascular permeability and the pathologic proliferation of retinal vessels. [2] Diabetic retinopathy DR is commoner in type 1 than in type 2 diabetes mellitus.

Platelets and blood viscosity

The variety of haematologic abnormalities seen in diabetes, such as increased blood viscosity, red blood cells sludging and aggregation, increased levels of fibrinogen and diminished fibrinolysis related to inhibition of plasmin by increased concentrations of α2-globulin or increased activity of tPA inhibitor type-1. High level of von Willebrand factor, increased production of thromboxane A2 and reduced prostacyclin production by endothelial cells favor platelet aggregation. Hyperglycaemia may represent a causal factor for in vivo platelet activation and may be responsible for nonenzymatic glycation of platelet glycoproteins, causing changes in their structure and conformation, as well as alterations of membrane lipid dynamics. [14]

Coagulation mechanism

Blood coagulation is a series of reactions in which plasma zymogens are converted into active enzymes. The final event of these reactions is the formation of an insoluble fibrin clot. These coagulant reactions are regulated by a number of stimulatory and inhibitory mechanisms. Thus, coagulation is a finely regulated system that maintains blood in a fluid phase, but can rapidly respond to injury for the formation of clots. Factor VII is a vitamin K–dependent serine protease glycoprotein (also known as stable factor or proconvertin) with a pivotal role in haemostasis and coagulation. Other vitamin K–dependent factors include prothrombin, factors IX and X, and proteins C and S. Tissue factor is an intrinsic membrane glycoprotein that is normally not exposed on the surface of intact blood vessels. When the vascular lumen is damaged, tissue factor is exposed and then binds to the small amounts of circulating factors VIIa and VII. This facilitates conversion of factor VII to factor VIIa. Factor VIIa bound to tissue factor in the presence of calcium and phospholipids facilitates the conversion of factor IX to factors IXa and X to factor Xa. Coagulation has traditionally been considered to occur via extrinsic and intrinsic pathways. Although this division is useful for understanding in vitro laboratory coagulation tests, no such division occurs in vivo because the tissue factor VIIa complex is a potent activator of factor IX and factor X. [15]

Several observations showed that vascular damage and endothelial dysfunction occurs early in the course diabetic microangiopathy. Increased endothelin-1 (ET-1) levels, increased plasma concentrations of tissue plasminogen activator (tPA) inhibitor, von Willebrand factor, fibrinogen, activated factor VII (FVII:c) and decreased concentrations of endothelium derived relaxing factor, prostacyclin, tPA and reduced fibrinolytic potential of vascular endothelium. The net effect of all these changes is to convert the endothelium from a thrombo-resistant to a thrombogenic surface and consequently, impairment of coagulation and of anticoagulant pathways. Coagulation and fibrinolytic abnormalities are stronger determinants of the presence of diabetic vascular complications. Coagulation profiles can be used to evaluate the incidence and assess the severity of diabetic retinopathy and other microangiopathies. Endothelin-1 (ET-1), a novel 21-amino acid vasoconstrictive peptide secreted by endothelial cells, has been thought to play a role in various forms of vascular disease. To investigate whether ET-1 levels may be related to microangiopathy in diabetes mellitus, plasma ET-1 levels were measured in two groups of diabetic patients, 47 patients with type 2 diabetes mellitus and retinopathy but without nephropathy and hypertension. In type 2 diabetes group the ET-1 concentration was significantly higher than both in the healthy subjects and type 1 diabetic patient. [15]

Objectives

General objectives: The main objective of this study is to assess the coagulation state in diabetic retinopathy in type 2 diabetic Sudanese patients

Specific objectives

1. To measure prothrombin time (PT) and activated partial thromboplastin time (APTT) in type 2 diabetic patients with diabetic retinopathy.
2. To estimate the level of factor VII: c in the plasma of type 2 diabetic patients who have different degrees of diabetic retinopathy.
3. To correlate between the severity of diabetic retinopathy with factor VII: c level.

METHODS

This is a case control hospital- based study was conducted at the Makkah eye complex in patients with type 2 diabetes mellitus and with diabetic retinopathy who were attending the retina referred clinic during the period of the study. They came from different areas of the Sudan. 40 patients with type 2 diabetes mellitus and with diabetic retinopathy and 10 healthy subjects serving as control group were investigated in this study and sample size was determined according to the availability of resources. Verbal consents were obtained from the patients and the control group after explanation of the purpose of the study. Data was collected using designed questionnaire including personal data of the patients, such as name, age, sex and residence as well as clinical information such as duration of diabetes and the drugs used for its management and drug history. Physical examination was done, including fundal examination by ophthalmoscope and slit

lamp, after dilation of the pupil by using mydriatics such as phenylophirin 10% or tropicamide eye drops, to assess the degree of diabetic retinopathy. 4.5ml of venous blood were collected from both patients and control, 2.25ml immediately delivered into two containers each containing 0.25ml of 13.3g/l aqueous tri sodium citrate for PT and APTT measurement, the rest of the plasma was delivered into cryo-tubes and stored at –80C and was used later in batches for FactorVII: c estimation.

RESULTS

Characteristics of the studied populations

Among the studied patients and the control group the ages ranged from 30 to 76 years. Six (12%) were between 30-40 years; five (10%) were between 41-50 years; fourteen (28%) were between 51-60 years; twenty (40%) were between 61-70 years, they represent the majority of the studied population. Only five (10%) were more than 70 years. Twenty-two (55%) patients were males and eighteen (45%) patients were females, in the control group six (60%) were males and four (40%) were females.

Clinical data

Two (5%) patients had diabetes for less than 10 years; twenty one (52.5%) patients for 10-20 years and seventeen patients were found to have diabetes for more than 20 years (42.5%) (Figure1).Twenty four (60%) patients had severe proliferative retinopathy; four (10%) patients had pre proliferative retinopathy and twelve (30%) patients had non proliferative retinopathy.
The correlation between the duration of diabetes and the degree of diabetic retinopathy revealed a highly significant correlation with p-value = 0.000. Odds Ratio (OR) =2.36. So, according to this the duration is a risk factor for the presence of diabetic retinopathy (Figure2).

Laboratory data

PT in diabetic patients and control group

Prothrombin time in patients and controls was arranged into three groups. Twenty seven patients had PT ranging from 11-13 seconds; which represents the majority of patients. Nine patients had PT ranging from 14-16 seconds and four patients had PT more than 16 seconds. In the control group four subjects had PT ranging from 11-13 seconds, six subjects had PT ranging from 14-16 seconds and no reading above 16 seconds was found in the control group (Tables 1). The correlation in PT mean values in diabetic patients and the control group revealed a positive correlation with P value <0.01 indicating a highly significant correlation (Table 2).

PT in different degrees diabetic retinopathies

Twenty (83%) patients out of twenty four with severe diabetic retinopathy had PT results ranging between 11-13 seconds, while only four (16.7%) patients had PT results ranging between14-16 seconds. In non-proliferative retinopathy seven (58.3%) patients had PT results between 11-13seconds, four (33.3%) patients had PT results between 14-16 seconds and one (8.4) patient had PT more than 16 seconds. In pre proliferative retinopathy three (75%) patients had PT results between 14-16 seconds and one (25%) patient with PT more than 16 seconds (Table 3). By using one way analysis of variance (ANOVA) to correlate between PT and different degrees of diabetic retinopathies, P-value=0.002 (highly significant).

Factor VII: c level in diabetic patients and control group

The entire control group had factor VII: c level between100-150%, twenty two (55%) patients had factor VII: c level within the same range. Eleven (27.5%) patients had factor VII: c level more than150%. Seven (17.5%) patients had factor VII: c level less than 100% (Table 4). Statistically the correlation between factor VII: c in diabetic patients and the control group revealed a significant correlation with P -value =0.03 (Figure 4).

Factor VII level in diabetic retinopathies

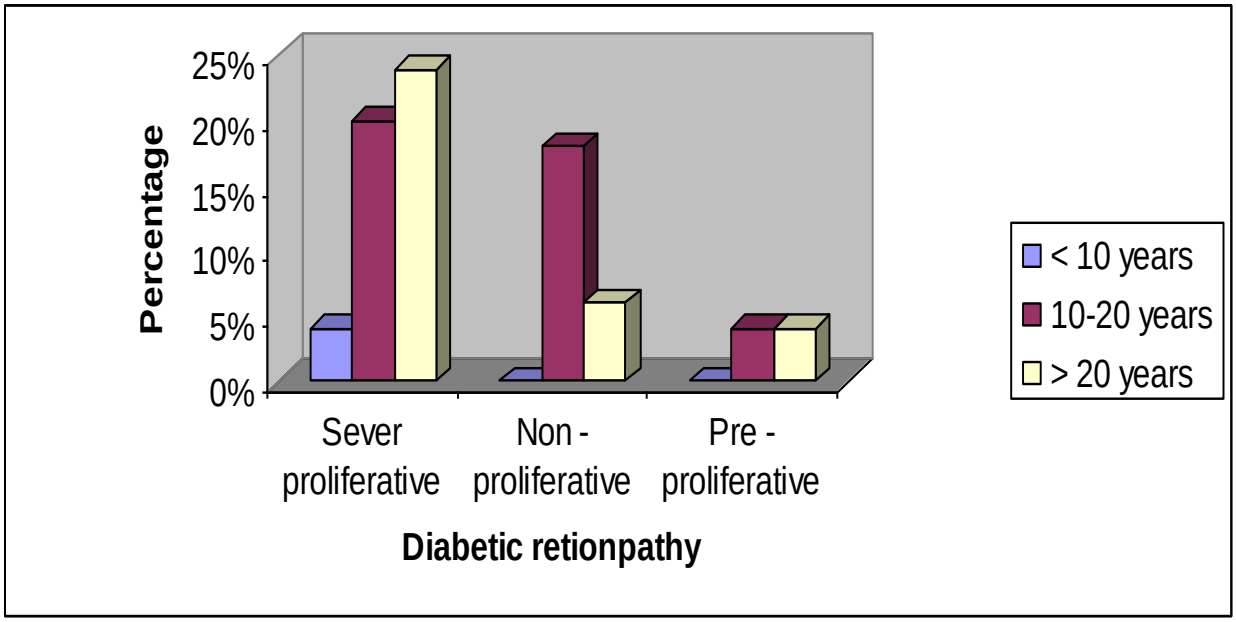
About nine (18%) patients with severe diabetic retinopathy had a factor VII level more than 150%, while in non-proliferative diabetic retinopathy patients only two (4%) had the same factor level. Neither patients with pre proliferative diabetic retinopathy nor the control group had factor VII levels more than 150% (Table 5).
Statistically, there is significant correlation between factor VII levels and diabetic retinopathy with p-value =0.019 and Odds Ratio (OR) = 0.27 (Figure 5)

APTT in diabetic patients and control group

Most of the patients thirty one (77.5%) and nine (90%) of the control group had APTT between 26-40 seconds (Table 6).
Statistically p-value=0.34 indicating that, there is no significant correlation between the disease and APTT.

APTT in diabetic retinopathy

Nineteen (79.2%) patients with severe diabetic retinopathy had an APTT level between 26-40 seconds and five (20.8%) patients had APTT less than 26 seconds. In preproliferative and non-proliferative retinopathy patients three (75%) and nine (75%) respectively, had an APTT level between 26-40 seconds (Table 7). The correlation between APTT and diabetic retinopathy revealed no significant result with a *p* value =0.98.



Chi- square = 55.334 P-value = 0.000 (P < 0.01, highly significant)
Odds Ratio (OR) = 2.36

Figure 1: The relationship between diabetic retinopathy and the duration of diabetes

Table 1: Prothrombin Time (PT) in patients and control group

PT (in sec)		Frequency	Percent
11 – 13	Case	27	67.5
	Control	04	40
14 – 16	Case	9	22.5
	Control	06	60
> 16	Case	04	010
	Control	-	-
Total	Case	50	100.0
	Control	10	100.0

Table 2: Relationship between the mean PT in diabetic patients and the control group

Factor	Mean		t-test	*P*-value
	Diabetic	Control		
PT	13.97	14.11	63.446	0.000 **

** P < 0.01, highly significant

Table 3: Prothrombin Time (PT) in different degrees of diabetic retinopathies

Diabetic retinopathies	PT group	
	11-13sec	14-16sec
Severe proliferative	20 (83%)	04 (16.2%)
Non- proliferative	07 (58.3%)	11 (33.3%)
Pre-proliferative	-	3 (75.0%)

P- value = 0.002, P< 0.01 highly significant)

Table 4: Factor VII level in diabetic patients and the control group

Factor VII level (%)	Patients	Percent	Control	Percent
<100	07	17.5	-	-
100 – 150	22	55.0	10.0	100.0
> 150	11	27.5	-	-

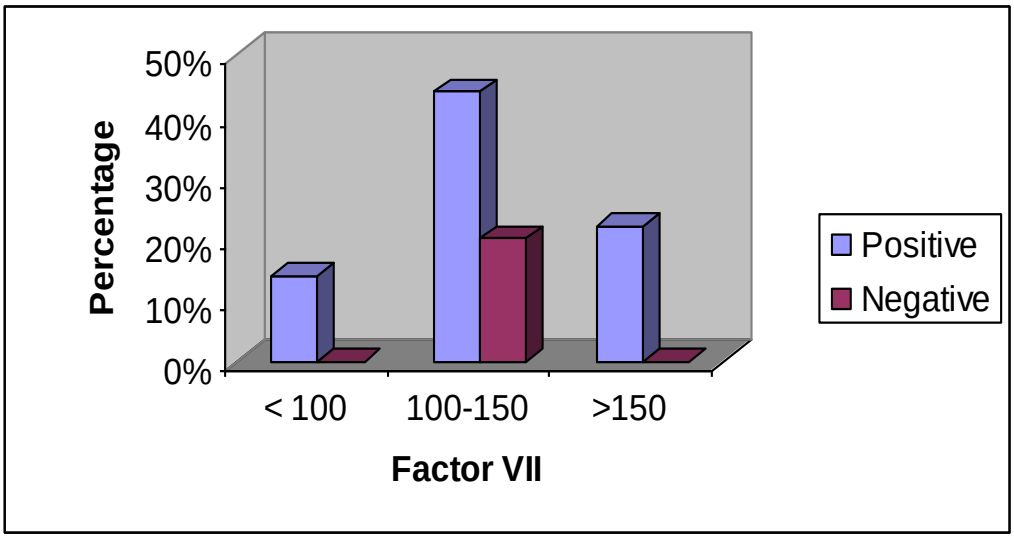


Figure 2: Factor VII: c in diabetic patients and the control group

P-value = 0.030 (P < 0.05, significant)

Table 5: Factor VII:c level in patients with diabetic retinopathy

Factor VII: c level (%)	Patients with diabetic retinopathy		
	Severe proliferative	Non proliferative	Pre proliferative
<100	2(4%)	3(6%)	2(4%)
100-150	13(26%)	7(14%)	2(4%)
>150	9(18%)	2(4%)	-
Total	24	12	4

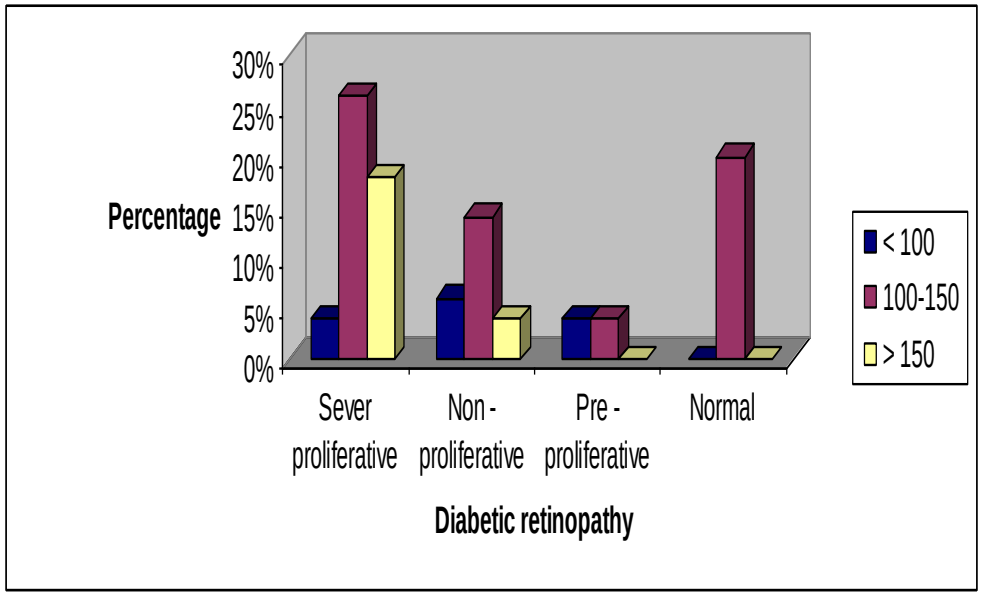


Figure 3: The relationship between diabetic retinopathy and factor VII: c Level

P-value = 0.019 (P < 0.05, significant)

Table 6: Activated partial thromboplastin time (APTT) in diabetic patients and the control group

Study population	APTT groups		Total
	<26sec	26-40sec	
Patients with diabetes mellitus	9(22.5%)	31(77.5)	40(100%)
Control group	1(10%)	9(90%)	10.(100%)

Table 7: Activated partial thromboplastin time (APTT) in diabetic retinopathy

Type of diabetic retinopathy	APTT groups		Total
	<26sec	26-40sec	
Severe proliferative	5(20.8%)	19(79.2)	24(100%)
Pre- proliferative	1(25%)	3(75%)	4(100%)
Non-proliferative	3(25%)	9(75%)	12(100%)

DISCUSSION

Insulin resistance and type 2 diabetes are associated with the development of endothelial dysfunction, enhanced platelet aggregation and activation, whilst the plasma levels of many clotting factors, including fibrinogen, factor VII, factor VIII, and factor XIII-b subunit is elevated. [16] This increased procoagulant activity is believed to be one of the factors that contribute to the high incidence of premature macro and microangiopathy and increased morbidity and mortality attributable to myocardial infarction, nephropathy and retinopathy observed in diabetic patients. [17] Thrombus formation results from disruption of the equilibrium between prothrombotic and anti-thrombotic factors that control clotting and haemostasis, this imbalance may occur due to an ongoing stimulus to thrombogenesis, a defect of natural anticoagulants or fibrinolysis. Pertubance of haemostasis has also been implicated in the development of microvascular complications such as nephropathy and retinopathy in diabetic patients. [18] The duration of diabetes affects the frequency of retinopathy. People who have had diabetes for about 20 years, nearly all of those with type 1 diabetes and 60% with type 2 diabetes had retinopathy. Moreover, after 25 years about 50% of people with type 1 diabetes have proliferative retinopathy compared with less than 10% of those with type 2 diabetes. In this study the duration of the disease had a highly significant correlation with the prevalence of retinopathy ($p<0.01$). Odds Ratio (OR) =2.36, indicating that the duration is a risk factor for the presence of diabetic retinopathy. This is in agreement with the Wisconsin epidemiologic study of diabetic retinopathy (WESDER). [19]

The present study also showed that type 2 diabetic patients had increased levels of factor VII: c in the plasma compared to the control group ($p=0.03$). This is in agreement with Ford et al [20]. There is evidence in the literature that, a direct correlation between fasting plasma glucose and factor VII level was found to exist in both diabetic and normal subjects. Induced hyperglycaemia was able to increase the factor VII level in both diabetic patients and normal control subjects while when euglycaemia was achieved in diabetic patients, factor VII level returned to normal. Factor VII level may be directly conditioned by circulating blood glucose and, therefore stresses the role of hyperglycaemia in conditioning coagulation abnormalities in diabetes mellitus. [21] The present study also revealed a significant relationship between factor VII: c level and diabetic retinopathy ($P=0.019$). There was marked increase in factor VII: c level in patients with severe proliferative retinopathy. This result has been documented by Fuller. J. H [22], in a study done in patients with type 1 and 2 diabetes mellitus. They found that diabetic patients with retinopathy had higher factor VII and anti-thrombin III values; and those with proteinuria had higher values for factor VII than those without this complication. There is evidence in the literature that, thrombogenic factors are related to urinary albumin excretion rate in type 1&2 diabetic patients. [23]

The present study showed that type 2 diabetic patients had shorter PT compared to the control group ($p<0.01$) indicating highly significant correlation. This is in agreement with Erem .C *et al.,* [24] in a study done in Turkey to investigate the markers of coagulation and fibrinolysis parameters in type 2 diabetic patients and their results demonstrated that the plasma levels of fibrinogen, AT III, PAI-1, vWF activity and PT were found to be significantly increased in the type 2 diabetic patients compared with the healthy subjects. Also HuJ *et al.,* [25] who observed that APTT and PT were shortened in diabetic patients as well as higher level of D- dimer, serum fibrin degradation product, median concentrations of fibrinogen and vWF. The present study also revealed a significant correlation between PT values and different degrees of diabetic retinopathy ($p<0.001$). This study also revealed no significant difference between the level of APTT in diabetic patients and the control group ($p=0.34$), this is in agreement with Fattah et al., [26] The correlation between APTT in different degrees of diabetic retinopathy revealed no significant result. ($p=0.098$). Coagulation and fibrinolytic abnormalities are stronger determinants of the presence of diabetic vascular complications than other clinical variables, including the degree of glycaemia, in stable, relatively well controlled patients with Type 2 diabetes. [27]

Good metabolic control could play a key role in controlling the coagulation irregularities in diabetes. However, considering the difficulties in achieving such an objective; it is possible that the use of drugs may represent a valid alternative. The Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) are two randomized clinical trials that conclusively showed the efficacy of glycaemic control in preventing diabetic retinopathy. [28]

CONCLUSION

This study concluded that patients with type 2 diabetes have an elevated level of factor VII: c in their plasma, the level of factor VII: c has a strong correlation with the severity of diabetic retinopathy, Factor VII: c level can be used as a monitor for the progression and severity of diabetic retinopathy, even before its onset and The prothrombin time is shorter in type 2 diabetic patients and also showed a significant correlation with the degree of diabetic retinopathy.

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