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Coagulation Profile in Diabetes and Its Association with Diabetic Microvascular Complications

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ABSTRACT

Objective: To investigate the hemostatic parameters and to assess their relationship with microvascular complications in patients with type-2 diabetes mellitus.

Study Design: Comparative cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan, from Jul to Dec 2020.

***Methodology*:** Patients with type-2 diabetes aged 40-70 years of both genders were included. We included sixty subjects with diabetes and sixty healthy individuals. HBA1c, prothrombin time, activated partial thrombin time, and fibrinogen levels were measured in both groups, and retinal photographs were taken.

Results: The platelet count was in the normal range for both groups but significantly lower in cases compared to controls (177.5±18.3 vs 231.2±18.1, p<0.001). Similarly, the mean fibrinogen level was significantly higher among cases compared to controls (298.2±11.4 vs 256.6±6.5, p<0.001). No significant difference was found between mean prothrombin time and activated partial thromboplastin time among the groups. Most complicated cases belonged to the group with more than 7% glycosylated haemoglobin compared to non-complicated cases (p<0.001). A significant association between the level of HBA1c and diabetic retinopathy was found.

Conclusion: The study showed that with a rise in glycemic index, the coagulation profile derangement occurs, with an increase in fibrinogen levels, decrease in platelets count and increase in microvascular complications.

Keywords: Fibrinogen, Prothrombin**,** Retinopathy.

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INTRODUCTION

Diabetes mellitus is a condition with high blood glycemic states, either due to a lack of insulin or insensitivity to insulin in the body.[1] Type-2 diabetes is the most common type of diabetes, which presents micro and macrovascular complications.[2,3] A likely cause attributed to these vascular damages is the presence of prothrombotic states among people with diabetes due to the involvement of activation of platelets and response of fibrinolytic systems.[4] Diabetic retinopathy (DR), if treated early, can prevent permanent blindness.[5] The prevalence of diabetes was recorded to be around 400 million people around the globe in the year 2017, subsequently increasing the risks of complications.[6,7] The data on the prevalence of diabetic retinopathy in Pakistan is inadequate. However, recent surveys and reports suggest that around 10 to 91 percent of individuals with diabetic retinopathy are among all patients with diabetes.[8] One of the factors associated with the development of DR includes coagulation profile disruption. This has recently gained importance. Agarwal *et al*.[9] reported an association of decreased prothrombin, activated partial thromboplastin time and fibrinogen levels, which were found to be more among the patients with ophthalmic retinal complications.

Diabetes is a complex disease which affects almost all the organs of the body. The rationale of the study was the close screening of preventable disorders associated with clotting and hemorrhagic complications by assessing the coagulation status of an individual for early detection of retinal complications. The objective of the study was to investigate the hemostatic parameters and to assess their relationship with microvascular complications in type-2 diabetes mellitus.

METHODOLOGY

The comparative cross sectional study was conducted at the (AFIO) Rawalpindi Pakistan from July to December 2020. The Ethical Committee approved the study (235/ERC/AFIO). A sample size of 60 was taken after calculation by the WHO calculator with an effect size of 0.8, 80% power, 95% confidence level and.[10]

Inclusion Criteria: Patients of either gender, aged 40 to 70 years with type-2 diabetes were included in the study. Healthy individuals of the same age group were matched for the study analysis having no type-2 diabetes or other comorbid conditions.

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Exclusion Criteria: Individuals with a history of hypercoagulability, such as thrombocytosis, known inherited coagulation disorders, venous thromboembolism, pregnancy, cancer, recent surgery, and hyperthyroidism were excluded. In addition, individuals on anticoagulation treatments or taking heparin or warfarin for other comorbidity were excluded. Patients with type-1 diabetes were also excluded from the study.

Patients with diabetes were further categorized based on glycosylated haemoglobin levels (HBA1c) as HBA1c levels ≤7% and HbA1c >7%.[11] Further, the groups were assessed based on the classification of retinopathy as proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR).[12] The HBA1c levels were assessed using an automated analyzer. The demographic data of the patients comprised the age of the patients, gender and duration of disease. All venous samples were collected in vacutainers with Ethylenediaminetetraacetic acid (EDTA) under aseptic conditions. Samples were sent to the laboratory, and levels of HBA1c, prothrombin time, activated partial thrombin time, and fibrinogen levels were measured using an automated analyzer and clotting-based automated analyzer, respectively. Retinal photographs were graded for the detection of diabetic retinopathy by using Optos imaging. The complications were graded as proliferative diabetic retinopathy or non-proliferative diabetic retinopathy based on the extent of microvascular complications.

The data were analyzed using SPSS-21.0. Quantitative variables were summarized as mean±SD and qualitative variables were summarized as frequency and percentages. The mean values were compared between cases and controls with the help of independent samples t-test, while categorical comparisons were made using the Chi-square test. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

There were 60 patients with diabetes type-2 referred to as cases, and 60 healthy individuals with no diabetes were grouped as controls in the study. Out of 60 cases, there were 29(48.3%) patients with diabetes with proliferative diabetic retinopathy complication. The mean disease duration for patients with diabetes was 11.1±6.2years (range 1-26years) (Table-I). Although the platelet count was in the normal range for both cases and controls, it was lower in cases than in controls (177.5±18.3 vs 231.2±18.1, $p<0.001$). Similarly, the mean fibrinogen level was significantly higher among cases compared to controls (298.2±11.4 vs 256.6±6.5, $p<0.001$) (Table-II).

Table-I: Summary of Baseline Characteristics of Cases and Controls (n=120)

Baseline Characteristics	Cases (n=60)	Controls (n=60)	*p*-value
Age(Mean±SD)	59.9±6.2	64.2±8.7	0.002
Age Groups			
45-55 years	14(23.3%)	11(18.3%)	0.009
56-65 years	32(53.3%)	19(31.7%)	
>65 years	14(23.3%)	30(50.0%)	
Gender			
Male	37(61.7%)	39(65.0%)	0.705
Female	23(38.3%)	21(35.0%)	

Table-II: Comparison of Coagulation Profile Between Cases and Controls (n=120)

Parameters	Study Groups		*p*-value
	Cases (n=60)	Controls (n=60)	
Platelet count (109/L)	177.5±18.3	231.2±18.1	<0.001
Prothrombin Time (secs)	13.7±0.6	13.8±0.6	0.661
Activated Partial Thromboplastin Time (Secs)	32.4±0.9	32.3±0.9	0.920
Fibrinogen (mg/dL)	298.2±11.4	256.6±6.5	<0.001

The mean HBA1c for patients with proliferative diabetic retinopathy was 9.2±1.6 compared to 6.7±0.1 for patients without complications ($p<0.001$). Similarly, most complicated cases belonged to a group with more than 7% glycosylated haemoglobin compared to non-complicated cases ($p<0.001$). The duration of diabetes in years was also significantly longer for complicated cases compared to others (16.1±5.2 vs 6.5±2.5, $p<0.001$) (Table-III).

Table-III: Comparison of Coagulation Profile of Cases with or without Complications (n=60)

Parameters	Cases with or Without Complications		*p*-value
	Complications (n=29)	No Complications (n=31)	
Glycated Hemoglobin (HbA1c)			
≤7%	1(3.4%)	28(90.3%)	<0.001
>7%	28(96.6%)	3(9.7%)	
Duration of diabetes (years)	16.1±5.2	6.5±2.5	<0.001
Platelet count (109/L)	173.2±16.6	181.6±19.0	0.078
Prothrombin Time (secs)	13.6±0.6	13.7±0.6	0.906
Activated Partial Thromboplastin Time (secs)	32.5±1.0	32.3±0.8	0.595
Fibrinogen (mg/dL)	306.6±7.6	290.3±8.3	<0.001

DISCUSSION

Our results reflected that higher HBA1c levels might be associated with PDR in patients with longer disease duration. This was similar to the results of Zhang *et al*.[13] who concluded that a longer duration of disease and higher HBA1c are associated with micro-vascular complications. However, their results showed younger age group might face more complications than the older age group. Our results showed a similar trend, with the levels of HBA1c being more among patients with complications. In addition, patients having higher HBA1c presented with more retinal complications.

Another study by Tan *et al*.[14] suggested that ethnicity, disease duration, and HBA1c levels were independent risk factors for developing diabetic retinopathy. Similarly, other studies suggested similar findings of higher HBA1c associated with a higher prevalence of diabetic retinopathy in people with diabetes.[15] This was similar to our results that around 28% of individuals with HBA1c higher than 7 presented with more complications. In addition, our study sample showed a mean age of 59.9±6.2 years for patients with diabetes with a longer duration of disease (p=<0.001).

Knowledge about diabetic retinopathy and its association with diabetic parameters helps early screening of DR and related blindness. In addition, it has been reported in the literature that diabetic retinopathy may develop with effective or aggressive management of glycemic control of any individual with diabetes. A preexisting mild diabetic retinopathy may become a complicated stage with aggressive or large blood glucose level reductions. Since the mechanisms are yet speculative, the screening is often neglected.[16,17]

Results from Agarwal *et al*.[9] showed a mean age of fifty to fifty-five in the two groups, similar to our study. They reported that as compared to healthy controls, patients with diabetes had more HBA1c levels and duration of disease and also had higher complications, with the individuals having higher parameters. Furthermore, the coagulation profile differed among the healthy and diseased groups. Activated partial thromboplastin time and prothrombin time were lower, contrary to our results, where we did not find any difference in the APTT levels in the two groups. Fibrinogen levels were found to be raised in the study, which was similar to our study results (p=<0.001). An association between the HBA1c levels was also noticed in the study, where higher HBA1c was found to be associated with deranged PT, APTT and fibrinogen levels. In addition, similar data were reported for patients with more retinal complications compared to the non-complication group.[18,19]

It has been mentioned in literature by FU *et al*.[4] that shortened APTT is considerable for the risk of hypercoagulability states. The possible reason is the glycation of red blood cells, prothrombin, and fibrinogen, which lead to coagulation abnormalities in patients with diabetes. Further presence of shorter APTT was significantly found to be associated with the patients with diabetes as compared to controls (p<0.001). However, the study was done in a limited time, on a smaller sample. Further research over a bigger sample covering both diabetes type-1 and type-2 may facilitate further understanding of the change in the parameters leading to microvascular complications among patients with diabetes.

CONCLUSION

The study showed that with the rise in glycemic index, the coagulation profile derangement occurs, with an increase in fibrinogen levels, decrease in platelet count and increase in microvascular complications. More research on the association of these parameters is warranted to ensure a guideline from basic tests to rule out at-risk individuals for the development of retinopathy. This may prevent individuals from sight-threatening complications.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AK & AR: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

SK & MHS: Data acquisition, data analysis, concept, critical review, approval of the final version to be published.

MST & MN: Critical review, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Forouhi NG, Wareham NJ. Epidemiology of diabetes. Medicine (Abingdon) 2014; 42(12): 698-702. doi: 10.1016.126542/j.mpmed.2014.09.007.
2. Faselis C, Katsimardou A, Imprialos K, Deligkaris P, Kallistratos M, Dimitriadis K. Microvascular Complications of Type 2 Diabetes Mellitus. Curr Vasc Pharmacol 2020; 18(2): 117-124. doi: 10.2174/1570161117666190502103733.

3. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol 2021; 69(11): 2932-2938. doi: 10.4103/ijo.IJO_1627_21.
4. Fu G, Yan Y, Chen L, Zhang M, Ming L. Shortened Activated Partial Thromboplastin Time and Increased Superoxide Dismutase Levels Are Associated with Type 2 Diabetes Mellitus. Ann Clin Lab Sci. 2018 ; 48(4): 469-77.
5. Choo PP, Md Din N, Azmi N, Bastion MC. Review of the management of sight-threatening diabetic retinopathy during pregnancy. World J Diabetes 2021; 12(9): 1386-1400. doi: 10.4239/wjd.v12.i9.1386.
6. Mumtaz SN, Fahim MF, Arslan M, Shaikh SA, Kazi U, Memon MS. Prevalence of diabetic retinopathy in Pakistan; A systematic review. Pak J Med Sci 2018; 34(2): 493-500. doi: 10.12669-120/pjms.342.13819.
7. Huang JX, Liao YF, Li YM. Clinical Features and Microvascular Complications Risk Factors of Early-onset Type 2 Diabetes Mellitus. Curr Med Sci 2019; 39(5): 754-758. doi: 10.1007/s11596-019-2102-7.
8. Afghani T, Khan SB, Mansoor H, Nisar S, Waseem S. Assessment of diabetic retinopathy and diabetes management systems in Pakistan using a WHO tool. J Pak Med Assoc 2020 ; 70(9): 1619-1624. doi: 10.5455/JPMA.12450.
9. Agarwal C, Bansal K, Pujani M, Singh K, Chauhan V, Rana D et al. Association of coagulation profile with microvascular complications and glycemic control in type 2 diabetes mellitus - a study at a tertiary care center in Delhi. Hematol Transfus Cell Ther 2019;41(1):31-36. doi: 10.1016/j.htct.2018.05.002.
10. Madan R, Gupt B, Saluja S, Kansra UC, Tripathi BK, Guliani BP. Coagulation profile in diabetes and its association with diabetic microvascular complications. J Assoc Physicians India 2010; 58(1): 481-484.
11. Aftab M, Ramzan A, Bhatti SH, Ahmad T, Raza MA, Shah SMA, et al. Correlates of diabetic retinopathy: A case study. Pak J Pharm Sci 2019; 32(4): 1909-1912.
12. Liu Y, Song Y, Tao L, Qiu W, Lv H, Jiang X, et al. Prevalence of diabetic retinopathy among 13473 patients with diabetes mellitus in China: a cross-sectional epidemiological survey in six provinces. BMJ Open 2017; 7(1): e013199.
13. Zhang G, Chen H, Chen W, Zhang M. Prevalence and risk factors for diabetic retinopathy in China: a multi-hospital-based cross-sectional study. Br J Ophthalmol 2017; 101(12): 1591-1595. doi: 10.1136/bjophthalmol-2017-310316.
14. Tan GS, Gan A, Sabanayagam C, Tham YC, Neelam K, Mitchell P, et al. Ethnic Differences in the Prevalence and Risk Factors of Diabetic Retinopathy. Ophthalmology 2018; 125(4): 529-536. doi: 10.1016/j.ophtha.2017.10.026.
15. Song P, Yu J, Chan KY, Theodoratou E, Rudan I. Prevalence, risk factors and burden of diabetic retinopathy in China: a systematic review and meta-analysis. J Glob Health 2018; 8(1): 010803. doi: 10.7189/jogh.08.010803.
16. Anwar SB, Asif N, Naqvi SAH, Malik S. Evaluation of multiple risk factors involved in the development of Diabetic Retinopathy. Pak J Med Sci 2019; 35(1): 156-160. doi: 10.12669/pjms.35.1.279
17. Bain SC, Klufas MA, Ho A, Matthews DR. Worsening of diabetic retinopathy with rapid improvement in systemic glucose control: A review. Diabetes Obes Metab 2019; 21(3): 454-466.
18. Simó-Servat O, Hernández C, Simó R. Diabetic Retinopathy in the Context of Patients with Diabetes. Ophthalmic Res 2019; 62(4): 211-217. doi: 10.1159/000499541.
19. Ephraim RK, Awuku YA, Adu P, Ampomah LT, Adoba P, Panford S, et al. High risk of coagulopathy among Type-2 Diabetes Mellitus clients at a municipal hospital in Ghana. Ghana Med J 2017; 51(3): 101-107. doi: 10.4314/gmj.v51i3.2.

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