

Original Research Article

Fibrinogen levels in type II diabetes mellitus patients with microvascular complications

Vijayalakshmi Chikkamath, Arathi Darshan, Jayaprakash S. Appajigol*,
Naveen Angadi, Abhishek T. G.

Department of Medicine, Jawaharlal Nehru Medical College, Belgaum, Karnataka, India

Received: 20 August 2018

Revised: 30 August 2018

Accepted: 26 September 2018

*Correspondence:

Dr. Jayaprakash S. Appajigol,

E-mail: jayaprakashappajigol@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Diabetes increases the morbidity and mortality due to its propensity to develop micro and macrovascular complications. Recently the role of haemostatic factors, particularly fibrinogen, in atherosclerosis and its complications has invited considerable attention. The present study was conducted to study plasma fibrinogen levels in type II diabetes mellitus patients with microvascular complications.

Methods: One hundred patients aged 18years to 60years with type 2 diabetes mellitus with microvascular complications were included in the study. HbA1c, plasma fibrinogen, urine routine examination, fundoscopy, monofilament testing, FBS, PPBS were done. Descriptive statistics was used to analyse data.

Results: Out of 100 diabetes patients with microvascular complication studies, 88 patients were found to have hyperfibrinogenemia. Out of 100 patients 67 patients had HbA1c of more than 8%, and all of them had elevated fibrinogen levels ($p < 0.0001$). The prevalence of hyperfibrinogenemia was higher in patients with diabetic retinopathy (90%), when compared to those without diabetic retinopathy (83.33%) although it was statistically not significant ($p=0.266$).

Conclusions: Hyperfibrinogenemia among type 2 diabetes mellitus patients with microvascular complications was high. Glycaemic control has a significant impact on the fibrinogen levels. Longer the duration of diabetes, there was a higher prevalence of hyperfibrinogenemia.

Keywords: Diabetes, Hyperfibrinogenemia, Microvascular complications

INTRODUCTION

The prevalence of diabetes has increased over the past decade and has been predicted to increase in the future. According to WHO, about 180 million people have diabetes. According to the current trend, more than 360 million people will have the disease by 2030.¹ The prevalence of both type 1 and type 2 diabetes mellitus is increasing worldwide, but the prevalence of type 2 diabetes mellitus is expected to rise exponentially in future because of increasing obesity and reduced activity levels.² Diabetes increases the morbidity and mortality

due to its propensity to develop micro and macroangiopathy.³

Diabetes has a major and deleterious impact on both individual and national productivity. Complications from diabetes such as coronary artery and peripheral vascular disease, stroke, diabetic neuropathy, renal failure, and blindness are resulting in increasing disability, reduced life expectancy. In the past decade, the suspected role of haemostatic factors, particularly fibrinogen, in atherosclerosis and its complications has invited considerable attention. Studies have shown that in acute

myocardial infarction, formation of an occlusive thrombus, on a damaged atherosclerotic lesion is the most common precipitating factor. Evidence also suggests that fibrinogen has a role, both in the early stages of plaque formation and late complications of cardiovascular disease.⁴

Recently increased attention is being paid to, disordered haemostatic mechanism in pathogenesis of both large and small vessel disease in diabetes.⁵ Impaired glucose tolerance and chronic hyperglycaemia exerts an influence on the pathogenesis of microvascular complications by increasing the thrombogenic factors like fibrinogen.⁶ Cardiovascular complications account for nearly 50% of deaths in type 2 diabetes mellitus and 25% in type 1 patients.

The present study was conducted to study plasma fibrinogen levels in type II diabetes mellitus patients with microvascular complications and find the association of plasma fibrinogen levels with glycaemic control.

METHODS

This is one-year cross sectional study of 100 patients from January 2016 to December 2016 conducted in the KLEs Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Type 2 Diabetes mellitus participants with age group between 18 to 60years and who were suffering from microvascular complication like retinopathy, nephropathy or neuropathy were included in the study. Patients with history of cigarette smoking, pregnant ladies, patients with ongoing infections, active malignancy and acute coronary or cerebrovascular events were excluded from the study.

After obtaining a written informed consent from all the patients, the candidates fulfilling the inclusion criteria were included in the study. The study participants were subjected to detailed history taking and physical examination. Routine blood tests like complete blood count and other tests needed for the study like HbA1c, plasma fibrinogen, urine routine examination, funduscopy, monofilament testing, FBS, PPBS were done.

Statistical analysis

Descriptive statistics was used to analyze data. Data were analyzed with the software named Statistical Package for the Social Science (SPSS) version 16.0.

RESULTS

In present study, among 100 patients, 33 were females (33%) and 67 were males (67%). There were 9 patients in the age group of 40-45years, 12 patients in the age group of 46-50years, 24 patients in the age group of 51-55years

and 55 patients in the age group of 56-60years. Out of 100 diabetes patients with microvascular complication studies, 88 patients were found to have hyperfibrinogenemia (fibrinogen levels more than 360 mg/dl). Among the patients who had hyperfibrinogenemia, 29 were females (32.95%) and 59 were males (67.04%). Out of 100 patients 67 patients had HbA1c of more than 8%, and all of them had elevated fibrinogen levels ($p < 0.0001$).

Duration of diabetes had remarkably impacted fibrinogen levels. Significant number of patients with more than 5 years of diabetes history had hyperfibrinogenemia (Table 1). Microvascular complications of diabetes, retinopathy, nephropathy and neuropathy was seen in 70%, 68% and 6% respectively. Diabetic retinopathy was more common with increasing duration of diabetes. Among the diabetic retinopathy patients 57 (73%) were more than 5 years of duration of diabetes. Similarly, diabetic nephropathy was more common with increasing duration of diabetes. Out of the 68 diabetes nephropathy patients, 55 (80.88%) patients were having diabetes from more than five years. Diabetic neuropathy was also more common among patients with diabetes of more than 5 years. Out of 6 diabetes neuropathy patients, four (66.66%) patients were diabetic from more than five years.

Table 1: Duration of diabetes and hyperfibrinogenemia.

Duration of DM (years)	Hyperfibrinogenemia	% of patients with hyperfibrinogenemia
≤ 5 years	12	13.63
>5 years	76	86.36

The prevalence of hyperfibrinogenemia was higher in patients with diabetic retinopathy (90%), when compared to those without diabetic retinopathy (83.33%) although it was statistically not significant ($p=0.266$). The mean levels of plasma fibrinogen in patients with diabetic nephropathy were 561.13mg/dl which was lower to that seen in patients without diabetic nephropathy which was 618.78mg/dl ($p=0.2265$). The mean levels of plasma fibrinogen in patients with diabetic neuropathy were 654.33mg/dl which was higher to that seen in patients without diabetic neuropathy which was 574.81mg/dl ($p=0.3966$).

DISCUSSION

Diabetes mellitus is considered to be associated with a state of hypercoagulability.^{7,8} Elevated plasma fibrinogen levels are thought to contribute significantly to this hypercoagulability.⁹ Fibrinogen studies and various other studies have found that increased fibrinogen levels are associated with major systemic illnesses like coronary artery disease, stroke etc. Diabetes is associated with low grade inflammation and as a result interleukin 6 are

elevated in these patients. This cytokine stimulates hepatocytes to produce fibrinogen representing an important link between inflammation and hypercoagulation.¹⁰ An association between the oxidative stress and levels of fibrinogen has been observed in diabetics. Fibrinogen synthesis is regulated by a feedback mechanism by thrombin activation. Thrombin formation is stimulated by free radicals in diabetic patients.¹¹ Hyperglycemia and insulin resistance and the oxidative stress may give rise to increased thrombin formation. In present study, authors found that the hyperfibrinogenemia was present 88% of diabetes patients with microvascular complications.

Hyperfibrinogenemia in diabetes has been reported to be caused by an increased synthesis of fibrinogen which is not compensated by a proportionate increase in the clearance of fibrinogen. This abnormality is associated with insulin deficiency and have been corrected with insulin suggesting that hyperfibrinogenemia is an indirect indicator of poor glycemic control.¹²

The correlation between glycemic control and fibrinogen levels could be due to (a) glycosylate fibrinogen is less susceptible to degradation by plasmin (b) relative insulin deficiency in diabetic patients results in differential protein synthesis i.e., 29% decrease in albumin synthesis and 50% increase in fibrinogen synthesis.¹³

In present study, authors found a positive correlation between the levels of plasma fibrinogen and HBA1c, suggesting that higher the HBA1c levels, higher is the plasma fibrinogen levels. Similar results were found in previous studies conducted by Fujii et al, and Van Wersch et al, respectively.^{14,15} In present study, the prevalence of diabetic retinopathy was 94%, diabetic nephropathy was 68% and diabetic neuropathy was 6%. Thus, the most common microvascular complication in our study was diabetic retinopathy. In present study, authors also found a positive association between the duration of diabetes and fibrinogen levels which was similar to that found in other studies conducted by Bruno G et al.¹⁶

In present study, authors also found a positive association between the duration of diabetes mellitus and the prevalence of diabetic retinopathy, but it was not statistically significant. As the duration of diabetes mellitus increased, the prevalence of diabetic retinopathy also increased. This finding was similar to that found in other studies.^{17,18} Authors also found a positive association between the duration of diabetes mellitus and diabetic nephropathy, but the association was not statistically significant.

CONCLUSION

On the basis of the observations made in our study, we conclude that the prevalence of hyperfibrinogenemia among type 2 diabetes mellitus patients with

microvascular complications was high. Authors also found a positive association between HBA1c levels and fibrinogen levels i.e., the higher the HBA1c the higher was the fibrinogen, indicating that glycaemic control has a significant impact on the fibrinogen levels. Through present study, authors also found a positive association between the duration of diabetes and fibrinogen levels. Longer the duration of diabetes, there was a higher prevalence of hyperfibrinogenemia. Thus, fibrinogen levels can be used as a marker for microvascular complications.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Alvin C Power. Diabetes mellitus. In: Kasper DL, Braunwald E, Fauci A, Hauser S, Longo D Jameson JL, eds. In: Harrison's Principle of Internal Medicine. 16th ed. McGraw-Hill;2004:3779-829
2. Alvin CP. Diabetes Mellitus. In: Braunwald E, Fauci AS, Kasper DL, Hauser SL, Longo DL, Larry JJ, eds. Harrison's principles of internal medicine, 15th ed. McGraw Hill Medical Publishing division, New York, 2001;2109-2137.
3. Mark A, Thomas F. Diabetes and vascular disease pathophysiology clinical consequences and medical therapy: Part I. Circulation. 2003 Sep 23;108(12):1527-32.
4. Bruno G, Cavallo-Perin P, Bargero G, Borra M, D'errico N, Pagano G. Association of fibrinogen with glycemic control and albumin excretion rate in patients with non-insulin-dependent diabetes mellitus. Ann Internal Med. 1996 Oct 15;125(8):653-7.
5. Fuller JH, Keen H, Jarrett RJ, Omer T, Meade TW, Chakrabarti R, et al. Haemostatic variables associated with diabetes and its complications. Br Med J. 1979 Oct 20;2(6196):964-6.
6. Kannel WB, D'Agostino RB, Wilson PW, Belanger AJ, Gagnon DR. Diabetes, fibrinogen, and risk of cardiovascular disease: the framingham experience. American Heart J. 1990 Sep 1;120(3):672-6.
7. Vekasi J, Marton ZS, Kesmarky G, Cser A, Russai R, Horvath B. Hemorheological alterations in patients with diabetic retinopathy. Clin Hemorheol Microcirculation. 2001 Jan 1;24(1):59-64.
8. Shin S, Ku Y, Babu N, Singh M. Erythrocyte deformability and its variation in diabetes mellitus. Indian J Exp Biol. 2007;45:121-8.
9. Klein RL, Hunter SJ, Jenkins AJ, Zheng D, Semler AJ, Clore J, et al. Fibrinogen is a marker for nephropathy and peripheral vascular disease in type 1 diabetes: studies of plasma fibrinogen and fibrinogen gene polymorphism in the DCCT/EDIC cohort. Diabetes Care. 2003 May 1;26(5):1439-48.

10. Ajjan R, Grant PJ. Coagulation and atherothrombotic disease. *Atherosclerosis*. 2006 Jun 1;186(2):240-59.
11. Ceriello A, Giacomello R, Stel G, Motz E, Taboga C, Tonutti L, et al. Hyperglycemia-induced thrombin formation in diabetes: the possible role of oxidative stress. *Diabetes*. 1995 Aug 1;44(8):924-8.
12. Bembde A S. A study of plasma fibrinogen level in type-2 diabetes mellitus and its relation to glycemic control. *Indian J Hematol Blood Transfus*. 2012;28(02):105-8.
13. De Feo P, Gaisano MG, Haymond MW. Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. *J Clin Investigation*. 1991 Sep 1;88(3):833-40.
14. Fujii C, Sakakibara H, Kondo T, Yatsuya H, Tamakoshi K, Toyoshima H. Plasma fibrinogen levels and cardiovascular risk factors in Japanese schoolchildren. *J Epidemiol*. 2006;16(2):64-70.
15. Van Wersch JW, Westerhuis LW, Venekamp WJ. Coagulation activation in diabetes mellitus. *Pathophysiol Haemostasis Thrombosis*. 1990;20(5):263-9.
16. Bruno G, Cavallo-Perin P, Barger G, Borra M, D'errico N, Pagano G. Association of fibrinogen with glycemic control and albumin excretion rate in patients with non-insulin-dependent diabetes mellitus. *Ann Internal Medicine*. 1996 Oct 15;125(8):653-7.
17. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol*. 1984 Apr;102(4):520-6.
18. Palmberg P, Smith M, Waltman S, Krupin T, Singer P, Burgess D, et al. The natural history of retinopathy in insulin-dependent juvenile-onset diabetes. *Ophthalmol*. 1981 Jul 1;88(7):613-8.

Cite this article as: Chikkamath V, Darshan A, Appajigol JS, Angadi N, Abhishek TG. Fibrinogen levels in type II diabetes mellitus patients with microvascular complications. *Int J Adv Med* 2018;5:1428-31.