Turk J Hematol 2007; 24:18-22

RESEARCH ARTICLE

Fibrinogen concentration: A marker of cardiovascular disorders in Nigerians

Olutayo Ifedayo Ajayi, Adekunle Ademola Famodu, Efosa Oviasu

Departments of Physiology, University of Benin, Benin City, Edo State, Nigeria
✉ *ifedayo1@yahoo.com*

Received: *Feb 28, 2006* • ***Accepted:*** *Feb 08, 2007*

ABSTRACT

Fibrinogen, one of the most hemorheologically active plasma proteins, is associated with several cardiovascular risk factors, and the plasma concentration can alter dramatically during acute phase response and in a wide variety of clinical conditions. We have assessed fibrinogen levels in some known cardiovascular disorders, during usage of contraceptive pills, acute phase conditions and pregnancy. Our results from patients with various disease conditions indicate that fibrinogen levels are in the pathological range and are significantly higher than in healthy controls ($p<0.001$). It is concluded that although Africans have low predisposition to thrombosis, they may well be pre-disposed to abnormal fibrin formation which could lead to various thromboembolic complications.

Key Words: Fibrinogen, cardiovascular risk factor, Nigerians

INTRODUCTION

Several prospective studies have demonstrated that high plasma fibrinogen levels are associated with an increased risk of ischemic heart disease [1-7]. Recently, it has been shown that plasma fibrinogen can serve as a predictor of cardiovascular disease and a marker of thromboembolic complications [7]. These discoveries have prompted recommendations that fibrinogen estimations be included in the cardiovascular risk profile [8].

Significantly higher plasma fibrinogen levels have been described in subjects with cardiovascular risk factors such as diabetes mellitus [9,10], hypertension [11,12], stroke [13], and smoking [4]. It has been observed that fibrinogen concentration increased with age in males and significantly in male smokers and non-smoking females [4]. An increased viscosity has been shown to relate to the acute phase protein response during sickle cell disease (SCD) [14-16], stress [17], and in asthmatic patients [18,19]. It has also been observed that fibrinogen genotypes and gene-environment interaction contribute to arterial and venous diseases. Such evidence supports the concept that elevations in fibrinogen precede the onset of the acute phase reaction (APR) rather than follow it. Raised plasma fibrinogen level has been reported in subjects with a familial risk of coronary heart disease [11], but this association has been disputed [20].

Fibrinogen, the basic physiological function of which in hemostasis is the formation of a fibrin network, is a major determinant of whole blood viscosity at low-shear rates [21] and plasma viscosity [22]. Plasma fibrinogen has important clinical significance in that it influences phenomena such as red blood cell aggregation and blood viscosity after vascular surgery [23] and the development of deep venous thrombosis postoperatively [24].

In view of the low incidence of thromboembolic complications and cardiovascular disorders in the local African population [25,26], we report the plasma fibrinogen levels in patients with various known cardiovascular risk factors, with a view to detecting significant changes which may be of pathological importance.

MATERIALS and METHODS

Patients: Only outpatients of both sexes who gave informed consent to participate in the study were enrolled and all the subjects were Nigerians. Patients receiving treatment for malaria were excluded because of likely influence of this condition on fibrinogen levels.

The patient groups consist of 50 diabetic (D), 50 hypertensive (HP), 50 smokers (SM) and 50 stroke (SK) patients representing cardiovascular risk factor groups. Also included in the study were: 100 sickle cell patients in stable (n: 50) and crisis (n: 50) state (SS and SSC, respectively); 54 asthmatic patients in stable state (n: 27) (ASM) and during attack (n: 27) (SASM); 100 women on combined biphasic oral contraceptive pill (OCP) (0.3 mg norgestrel with 0.03 mg ethyl estradiol) for at least three months to three years; and 100 pregnant women.

Controls: One hundred normal healthy individuals (50 men, 50 women) who were normotensive, non-smoking, and non-diabetic with genotype AA served as controls. The hemoglobin genotype AA was specifically chosen for the controls to reduce any possible effect/contributions of either heterozygous or homozygous S-gene in acute phase reactions according to previous observations [14-16]. Both patients and controls were aged between 18 and 50 years, except in a few sicklers with lower age ranges, but none was less than 12 years.

Methods: 5 ml of blood was collected from the cubital vein using a plastic syringe while applying tourniquet lightly over the arm until blood flow was established. Stasis was avoided during blood collection to prevent activation of clotting factors. 4.5 ml of blood was transferred into a plastic tube containing 0.5 ml of 3.8% sodium citrate. Blood and anticoagulant were mixed gently but thoroughly. Plasma was separated by centrifugation at 3000 g for 5 minutes, and the supernatant plasma was removed for immediate laboratory analysis. Plasma fibrinogen was determined by the clot-weight technique of Ingram [27].

Statistics: Values are expressed as mean±SD. The significant difference between the means was determined by Student's t-test. P values less than 0.05 ($P<0.05$) were considered significant.

Odds ratios were calculated using the Bandolier method [28]. Any odds ratio greater than one indicates the likelihood of an event to happen.

Table 1. Fibrinogen levels in various disease conditions

	Fibrinogen Concentration (g/L) Range	*Mean ± SD*	*Odds Ratios*
Control (100)	1.0– 2.5	1.90 ± 0.05	
Diabetics (D) (50)	1.3 – 6.0	4.10 ± 0.01*	2.16
Stroke (SK) (50)	2.5 – 6.1	4.10 ± 1.55*	2.16
Hypertensive (HP) (50)	2.6 – 4.9	3.10 ± 1.01*	1.63
Smokers (SM) (50)	1.5 – 6.9	4.31 ± 0.18*	2.27
Sicklers in Crisis (SSC) (50)	3.0 – 9.0	5.50 ± 1.55*	2.89
Stable Sicklers (SS) (50)	2.1 – 6.0	4.19 ± 1.42*	2.20
Asthmatics during Attack (ASM) (27)	2.5 – 4.5	4.04 ± 0.86*	2.12
Stable Asthmatics (SASM) (27)	2.0– 4.0	3.66 ± 0.19*	1.93
OCP Users (100)	2.0 - 5.0	3.90 ± 1.03*	2.05
Pregnancy (100)	2.0 – 5.5	4.20 ± 0.90*	2.21

* P< 0.001

Table 2. Sex variations and fibrinogen concentrations

	MALE	*FEMALE*
Controls	1.8 ± 0.10	2.5 ± 0.12**
Diabetics	4.0 ± 0.06	5.2 ± 0.10**
Stroke	4.5 ± 0.10	5.8 ± 0.01**
Hypertension	2.85 ± 0.13	3.0 ± 0.10
Sicklers in crisis	4.39 ± 0.02	5.32 ± 1.13**
Stable sicklers	3.85 ± 0.15	4.1 ± 1.02
Asthmatics during attacks	3.55 ± 0.20	4.02 ± 1.12
Stable asthmatics	3.20 ± 0.15	3.52 ± 1.1

** P< 0.05

RESULTS

Table 1 shows the mean ± SD and range of fibrinogen concentrations and their odds ratios in patients with the selected cardiovascular risk factors (diabetics, hypertensives, smokers and stroke patients); chronic and acute phase of sickle cell disease and asthmatic attack; in women on OCP; and at various trimester stages of pregnancy. Plasma fibrinogen concentrations were significantly higher ($p<0.001$) than in controls.

Table 2 shows sex variations in fibrinogen concentrations. There were statistically significant increases in the female controls, diabetics, and stroke and sicklers in crisis ($P<0.05$ respectively).

DISCUSSION

Although epidemiologic studies in Caucasians have long demonstrated the strong and often independent direct correlation between high plasma fibrinogen levels and cardiovascular disorders, no study has investigated the relationship of fibrinogen level with cardiovascular risk factors in Africans. In this report, we studied a group of subjects suffering from cardiovascular risk factors, with the aim of investigating the relationship between fibrinogen and potential risks.

The values from this study indicate that plasma fibrinogen levels were significantly higher compared with controls and were in the pathological range in subjects prone to thromboembolic disorders [25,26]. Whether these findings are of clinical significance awaits further clarification, even more so since the Negroid Black African has been shown to be protected from thromboembolism and atherogenesis [29,30].

Our study confirms several previous observations on fibrinogen: levels are increased in diabetics, hypertensives, stroke patients, smokers, sickle cell disease, asthmatic attack, during pregnancy and in women on OCP [1-7,9-19]. Our smoking group was comprised of only males, because the smoking habit is significantly less in females than males in Nigeria. In our study, as in several others [6,7], smokers have higher fibrinogen levels. It therefore appears that smoking may influence the synthesis of fibrinogen.

There was a significant increase in plasma fibrinogen concentrations both in the chronic and acute state sickle cell disease [31] and in asthmatic conditions, but more significantly during the acute phase. The use of OCP has been associated with increased incidence of thromboembolism and enhanced fibrinogen and other coagulation factors [6,32]. As in our previous report [33], OCP do increase circulating fibrinogen and such increases were cumulative and directly dependent on the duration of usage. It was suggested that the raised fibrinogen levels in Nigerian women on OCP seem to be induced by OCP and decreased fibrinolysis in the presence of adequate fibrinogen synthesis by the liver. The latter assumption is supported by the finding of an enhanced spontaneous fibrinolytic activity in the Nigerian

male compared to the female [29,30], a factor these authors have attributed to a level of protection from atheroma and atherosclerosis in African males compared with Europeans.

This study revealed that the plasma fibrinogen concentration significantly increased during pregnancy compared to controls. The acute phase influence of fibrinogen is further re-iterated here.

In all cardiovascular diseases, inflammatory responses have been frequently documented by various workers, and these could be the outright signals for hyperfibrinogenemia in all the risk groups studied.

The odds ratios or risk ratios are favored in all the risk groups, which indicates a great likelihood for the occurrence of the potential risks associated with hyperfibrinogenemia. The odds ratios were greater than one in all cases studied.

In conclusion, fibrinogen levels in Nigerians are significantly higher in cardiovascular potential risk groups than their controls. The study, however, raises the question as to what levels of fibrinogen are critical to predispose Africans to cardiovascular complications. Further studies are needed to confirm our findings and we suggest that there is need for epidemiological study of Negroid Africans.

Acknowledgement

This research was supported in part by the University of Benin (URPC research grant to Professor A.A. Famodu).

References

1. Wilhelmsen L, Svardsudd K, Korsan-Bengtsen K, Larsson B, Welin L, Tibblin G. Fibrinogen as a risk factor for stroke and myocardial infarction. N Engl J Med 1984;311:501-15.
2. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA 1987;258:1183-6.
3. Ceriello A, Pirisi M, Giacomello R, Stel G, Falleti E, Motz E, Lizzio S, Gonano F, Bartoli E. Fibrinogen plasma levels as a marker of thrombin activation: new insights on the role of fibrinogen as a cardiovascular risk factor. Thromb Haemost 1994;71:593–5.
4. Giansante C, Fiotti N, Cattin L, Da Col PG, Calabrese S. Fibrinogen, D-dimer and thrombin–antithrombin complexes in a random population sample: relationships with other cardiovascular risk factors. Thromb Haemost 1994;71:581-6.
5. Stone MC, Thorp JM. Plasma fibrinogen--a major coronary risk factor. JR Coll Gen Pract 1985;35:565-9.
6. Meade TW, Mellows S, Brozovic M, Miller GJ, Chakrabarti RR, North WR, Haines AP, Stirling Y, Imeson JD, Thompson SG. Haemostatic function and ischemic heart disease: principal results of the Northwick Park Heart Study. Lancet 1986;2:533-7.
7. Heinrich J, Balleisen L, Schulte H, Assmann G, van de Loo J. Fibrinogen and factor VII in the prediction of coronary risk: results from the PROCAM study in healthy men. Arterioscle Thromb 1994;14:54-9.
8. Rosenson RS, Tangney CC, Itafner JM. Intra-individual variability of fibrinogen levels and cardiovascular risk profile. Arterioscler Thromb 1994;14:1928-32.
9. Reid HL, Obi CO, Oli JM. Reduced erythrocyte deformability and hyperfibrinogenemia in Nigerian diabetics with hemoglobin genotype HbAA. Acta Diabet Lat 1984;21:105-14.
10. Famodu AA, Ojogwu LI, Okpere BE, Idaewor M, Jaiyesimi AEA. Plasma fibrinogen and fibrinolytic activity in Nigerian diabetics treated with insulin. Nig Med J 1995;29:53-5.
11. Reid HL, Anah CO. Haemorheological parameters in hypertensive Nigerians with and without sickle cell trait. Angiology 1985;36:379-86.
12. Obasohan AO, Famodu AA, Aigbe AA. Abnormal fibrinolysis in Nigerian hypertensives. Trop Cardiol 1992;18:17-21.
13. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, Abbott R, Godwin J, Dyer A, Stamler J. Blood pressure, stroke and coronary heart disease. Lancet 1990;335:765-74.
14. Richardson SON, Breeze GR, Stuart J. Hyperfibrinogenaemia and hyperviscosity in sickle cell crisis. J Clin Path 1976;19:890-3.
15. Famodu AA, Reid HL. Plasma fibrinogen in sickle cell disease (HbSS). Trop Geogr Med 1987;39:36-8.
16. Famodu AA. Coagulation changes in homozygous sickle cell disease (HbSS). J Clin Path 1987;40:1487.
17. Reid HL, Chukwudebelu WO. Plasma fibrinogen response after Caesarian section in Nigerians. East Afr Med J 1984;16:765-8.
18. Famodu AA, Oviawe O, Falodun O. Haemorrheological changes in asthmatic Nigerian children. Haemotologia 1994;26:117-9.
19. Famodu AA. Haemorheological changes and fibrinolytic activity in adult asthmatic patients with sickle cell trait. Clin Hemorheol and Microcirc 1998;19:1-5.
20. Hamsten A, de Fair U, Iselius L, Blomback M. Genetic and cultural inheritance of plasma fibrinogen concentration. Lancet 1987;11:988-90.
21. Stuart J, Kenny MW. Blood rheology. J Clin Path 1980;33:417-27.

22. Harkness J. The viscosity of human blood plasma; its measurement in health and disease. Biorheology 1971;8:171-93.
23. Postlethwaite JC. The importance of plasma fibrinogen in vascular surgery. Ann Roy Coll Surg Engl 1976;58:457-60.
24. Dormandy JA, Edelmen JB. High blood viscosity: an aetiological factor in venous thrombosis. Br J Surg 1973;60:187-90.
25. Yarnell JW, Baker IA, Sweetnam PM, Bainton D, O'Brien JR, Whitehead PJ, Elwood PC. Fibrinogen, viscosity, and white blood cell count are major risk factors for ischemic heart disease. The Caerphilly and Speedwell collaborative heart disease studies. Circulation 1991;83:836-44.
26. Cremer P, Nagel D, Labrot B, Mann H, Muche R, Elster H, Seidel D. Lipoprotein Lp(a) as predictor of myocardial infarction in comparison to fibrinogen, LDL, cholesterol and other risk factors: results from the prospective Gottingen Risk Incidence and Prevalence Study (GRIPS). Eur J Clin Invest 1994;24:444-53.
27. Ingram GI. A suggested schedule for rapid investigation of acute haemostatic failure. J Clin Path 1961;4:356-60.
28. Bandolier. What is an odds ratio? Swots corner Mar 1996; 25-6. http://www.jr2.ox.ac.uk/bandolier band/b25-6.html25.
29. Essien EM. Enhanced fibrinolysis in Nigerians: probable contributory factor to low prevalence of atherosclerosis in Nigerians. Afr J Med Sci 1976;5:287-90.
30. Dupuy E, Fleming AF, Caen JB. Platelet function, factor VIII, fibrinogen and fibrinolysis in Nigerians and Europeans in relation to atheroma and thrombosis. J Clin Path 1978;31:1094-101.
31. Famodu AA, Adedeji MO, Reid HL. Serial plasma fibrinogen changes accompanying sickle cell crisis. Clin Lab Haematol 1990;12:43-7.
32. Famodu AA, Elom EU, Ehigiegba AE, Fakoya TA. Abnormal fibrinolytic activity in African women taking oral contraceptives. Blood Coag Fibrinolysis 1993;4:643.
33. Famodu AA. Serial changes in plasma fibrinogen concentration and fibrinolytic activity in African women on oral contraceptive pills (OCP). Afr J Repr Health 1997;2:60-6.