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Coagulation factors and antithrombin levels in young and elderly subjects in Pakistani population

Huma Amin^a, Shahida Mohsin^a, Maria Aslam^a, Shabbir Hussain^a, Tahir Saeed^a, M Ikram Ullah^b and Waqas Sami^c

Aging is associated with increased levels of coagulation factors and decrease in natural anticoagulant factors. This strongly supports that age-related hypercoagulable state occurs in elderly. This study aimed to measure the plasma levels of coagulation factors and anticoagulant levels in young and elderly to observe the effect of age on haemostatic system. Ninety healthy individuals, both men and women were divided into two groups on the basis of age. Group I included participants of less than 40 years of age, whereas, group II comprised of participants more than 60 years of age. Fibrinogen activity was assessed by using Clauss technique. Coagulation factor VII, and factor VIII activity by corresponding one stage assay based on prothrombin time and activated partial thromboplastin time. Antithrombin III was measured by the chromogenic method. Our results showed that significantly increased levels of fibrinogen ($P=0.001$) were observed in the elderly population as compared to young. Higher fibrinogen levels in younger women than men and comparatively higher level than other races was observed in our local population. Increase in factor VII levels ($P=0.05$) was also observed in the elderly group. This increase was statistically significant

with age in women ($P=0.03$). Factor VIII rose with age in both sexes ($P=0.001$). Higher antithrombin activity was observed in the younger group whereas the older group demonstrated significantly lower antithrombin activity ($P=0.001$). We conclude that considerable effects of age and sex are observed on coagulation factors and naturally occurring inhibitors. *Blood Coagul Fibrinolysis* 23:745–750 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Keywords: age-related changes, antithrombin, fibrinogen, factor VII, factor VIII, haemostatic system

^aDepartment of Haematology, ^bDepartment of Biochemistry and ^cDepartment of Biostatistics, University of Health Sciences, Lahore, Pakistan

Correspondence to Dr Shahida Mohsin, Assistant Professor, Haematology, University of Health Sciences, Lahore, Pakistan
E-mail: shahida.mohsin@yahoo.co.uk

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Introduction

The haemostatic system is a defense mechanism of the body to stop bleeding. It includes platelets and coagulation cascade tightly monitored by anticoagulants and the fibrinolytic system [1]. In healthy individuals as the age advances the aptitude of blood to coagulate also increases because of the increase in the plasma concentration of most procoagulant factors [2]. The remarkable increase in thrombotic events in the elderly population has prompted investigations of the haemostatic system to reveal the changes taking place with age [3].

An increment of plasma fibrinogen level by 10 mg/dl for each decade can be expected in healthy participants [4]. Elevated plasma fibrinogen is associated with increased risk for many diseases, such as, atherosclerosis, acute myocardial infarction and stroke [5].

Plasma level of factor VII *in vivo* gives a clear indication of the haemostatic balance between the extremes of haemorrhage and thrombosis [6]. Factor VII levels increases with age in both sexes [7]. It is indicated to be an independent risk factor of coronary heart disease (CHD) [8]. Factor VIII coagulant levels also increase progressively with age and its activity is reported to increase from 160 units/dl to over 200 units/dl in participants of 60 years [3]. Elevated plasma

levels of factor VIII are associated with an increased risk of venous thrombosis [9].

Antithrombin is a physiological inhibitor and an important regulator of the coagulation cascade. Some variations in normal ranges are noted, such as slightly lower levels are seen in elderly men and in women taking birth control pills [10].

Fibrinogen (Fbg) and factor VII may contribute to the cardiovascular risk due to their influence on blood viscosity, platelet aggregation, low-density lipoprotein deposition and cell proliferation [11]. Most of the factors that cause venous thromboembolism are related to changes in blood flow and changes in the composition of the blood. The risk of thrombosis increases linearly with the increase in plasma factors II, VIII, IX and XII levels [12].

The objective of this study was to compare levels of haemostatic factors between elderly participants undergoing the normal aging process with young participants. More knowledge of these haemostatic factors and their interaction with cardiovascular diseases and thrombosis might be used to individualize risk and develop therapeutic strategies for prevention.

Table 1 Demographic data from the participants included in the study

| | Group I (<40 years of age) | Group II (>60 years of age) |
|----------------------------------|-------------------------------|--------------------------------|
| Number of participants | 45 | 45 |
| Mean age of participants (years) | 27.7 ± 5.12 | 68.6 ± 8.61 |
| Range of age | 19–39 | 60–80 |
| Men/women | 19/26 | 27/18 |

Materials and methods

Prior to the start of the study, permission was obtained from the Ethical review Committee, University of Health Sciences, Lahore, Pakistan.

This cross-sectional comparative study was carried out in the department of Hematology, University of Health Sciences Lahore. Blood samples of 90 participants (46 men and 44 women) from the normal healthy population were taken over a period of 6 months. Participants within the range of ages: 18–40 years were included in group I. Volunteers meeting the inclusion criteria were enrolled in this group from University of Health Sciences, Lahore. Group II included participants, who were 60–80 years old. They were recruited from house-to-house survey targeting the geriatric population. Each respondent completed a survey questionnaire, which provided information on age, sex, history of acute and chronic illnesses and history of drug intake. Participants with positive history of diseases related to the arterial or venous vessels, cardiovascular diseases and any other chronic illness, pregnant women and women on hormone replacement therapy or taking hormonal contraceptive pills were excluded.

A sample was collected from each participant in the nonfasting state. Volunteers were requested to refrain from heavy meals and vigorous exercise from midnight beforehand. Blood was drawn to produce the proper 9:1 ratio of blood to anticoagulant. Blood samples were rapidly (within 60 min of blood collection) returned to the laboratory for separation of plasma. Platelet poor plasma (PPP) was separated by centrifugation, for 15 min at 2500g. Plasma was stored at -70°C and was used for assay in batches. Prior to testing, plasma was thawed at 37°C for not more than 5 min.

Fibrinogen levels in plasma of all participants were measured by the Clauss method [13]. Factor assay for factors VII and VIII was performed by one-stage assay

based on PT and APTT, respectively. Antithrombin quantitative assay was based on determination of antithrombin activity level in plasma by synthetic chromogenic substrate method.

Fibrinogen, factor VII, factor VIII and plasma antithrombin level data were expressed as mean ± SD. Two independent sample *t* test was used to test the difference between the means of two groups. A *P* value of 0.05 or less was considered as statistically significant difference between the two groups. Correlation between age and study variables was performed by calculating the Pearson's correlation coefficient. Values less than 0.01 were considered as statistically significant.

Results

The demographic data of ninety participants, divided according to age is outlined in Table 1. The mean levels of study variables in young and elderly irrespective of sex are summarized in Table 2. Mean concentration of fibrinogen and mean percentage activity of coagulation factors VII and VIII were lower in young group than in the elderly group. Difference between the two groups was statistically significant ($P < 0.01$), ($P = 0.05$) and ($P < 0.001$), respectively (Table 2).

Mean levels of study variables in young and elderly men and women (group I and II) are illustrated in Table 3. The magnitude of increase in fibrinogen level with advancing age was much greater in men as compared to the women. However, in contrast to men, plasma levels of factor VII increased with age in women significantly ($P = 0.03$). The rise in plasma levels of factor VIII activity (%) in men and women were significant in both groups. Both men and women showed a substantial decrease in antithrombin activity and this drop off was almost equal in both sexes (Table 3).

Compared with young men, higher levels of plasma fibrinogen were found in younger women ($P = 0.06$). Before the age of 40 years, the mean value of factor VII was slightly lower in women [$93.84\% \pm 16.08$ (mean ± standard deviation)] than men [$96.51\% \pm 13.07$] $P = 0.9$ (Table 3).

In contrast to the younger group, no major difference in fibrinogen levels was observed in men and women of the elderly age group. Regarding the mean plasma levels of factor VII contrary to young age, the mean levels were higher in women 114.7 ± 41.25 than in men 99.15 ± 98.42 , $P = 0.1$ after 60 years of age (Table 3).

Table 2 Mean values of the haemostatic variables in the two groups

| Study variable | Group I (young <40 years of age) | | Group II (elderly >60 years of age) | | <i>P</i> value |
|---------------------------|----------------------------------|--------------|-------------------------------------|----------|----------------|
| | Mean ± SD | Range | Mean ± SD | Range | |
| Fbg (mg/dl) | 312.3 ± 70.9 | 202–535 | 418 ± 93.0 | 206–652 | <0.001 |
| Factor VII (% activity) | 94.9 ± 14.8 | 65.6–127 | 105.4 ± 36.57 | 72.4–251 | 0.05 |
| Factor VIIIc (% activity) | 77.3 ± 11.25 | 46.60–100.70 | 110 ± 34.2 | 75–290 | <0.001 |
| AT (% activity) | 107.0 ± 29.04 | 70–233 | 83.45 ± 22.53 | 29–233 | <0.001 |

AT, antithrombin; Fbg, fibrinogen; group I, $n = 45$; group II, $n = 45$.

Table 3 Mean values of the haemostatic variables in young and old men and women

| Study variable | Group I (young <40 years of age) | | Group II (elderly >60 years of age) | | P value |
|---------------------------|----------------------------------|-------------|-------------------------------------|-------------|---------|
| | Mean ± SD | Range | Mean ± SD | Range | |
| Young and old men | | | | | |
| Fibrinogen (mg/dl) | 289.7 ± 61.03 | 202–420 | 420.63 ± 98.42 | 206–652 | 0.00 |
| Factor VII (% activity) | 96.5 ± 13.07 | 74.1–120 | 99.15 ± 98.42 | 72.4–177.4 | 0.49 |
| Factor VIIIc (% activity) | 76.83 ± 11.80 | 61.90–100.7 | 112.09 ± 41.13 | 80.8–290 | 0.00 |
| Antithrombin (% activity) | 107.20 ± 35.44 | 70–142 | 82.70 ± 22.51 | 28–121 | 0.02 |
| Young and old women | | | | | |
| Fibrinogen (mg/dl) | 328.85 ± 74.06 | 212–535 | 414.50 ± 87.05 | 269–535 | 0.001 |
| Factor VII (% activity) | 93.84 ± 16.08 | 65.6–127 | 114.7 ± 41.25 | 73.2–251 | 0.03 |
| Factor VIIIc (% activity) | 77.70 ± 11.05 | 46.6–93.0 | 104.07 ± 41.25 | 74.3–138.30 | 0.00 |
| Antithrombin (% activity) | 106.61 ± 19.15 | 76.0–233.0 | 84.33 ± 22.54 | 34.0–115.0 | 0.02 |

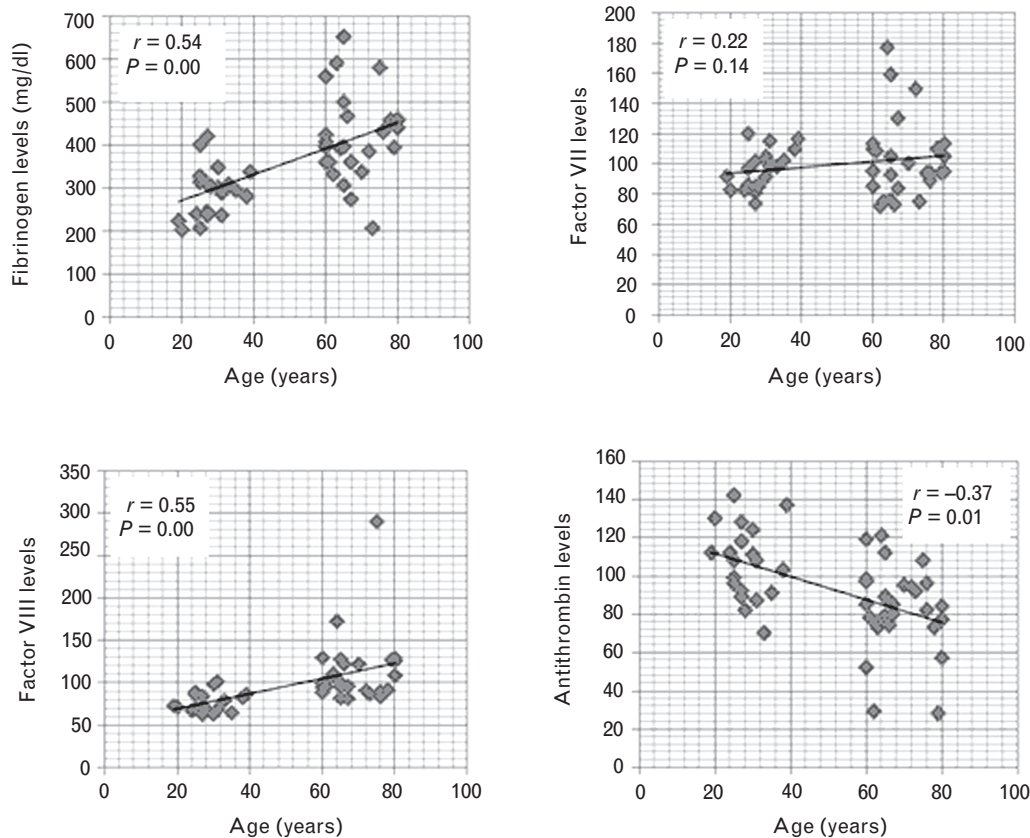
Men: group I, n = 19; group II, n = 27. Women: group I, n = 26; group II, n = 18.

Pearson correlation of haemostatic variables with age was also studied (Figs 1 and 2). Fibrinogen and factor VIII showed positive correlations with age. factor VII, although showed positive correlation but magnitude of this correlation was fairly weak ($r=0.20$). Antithrombin demonstrates negative correlations with age (Table 4).

Discussion

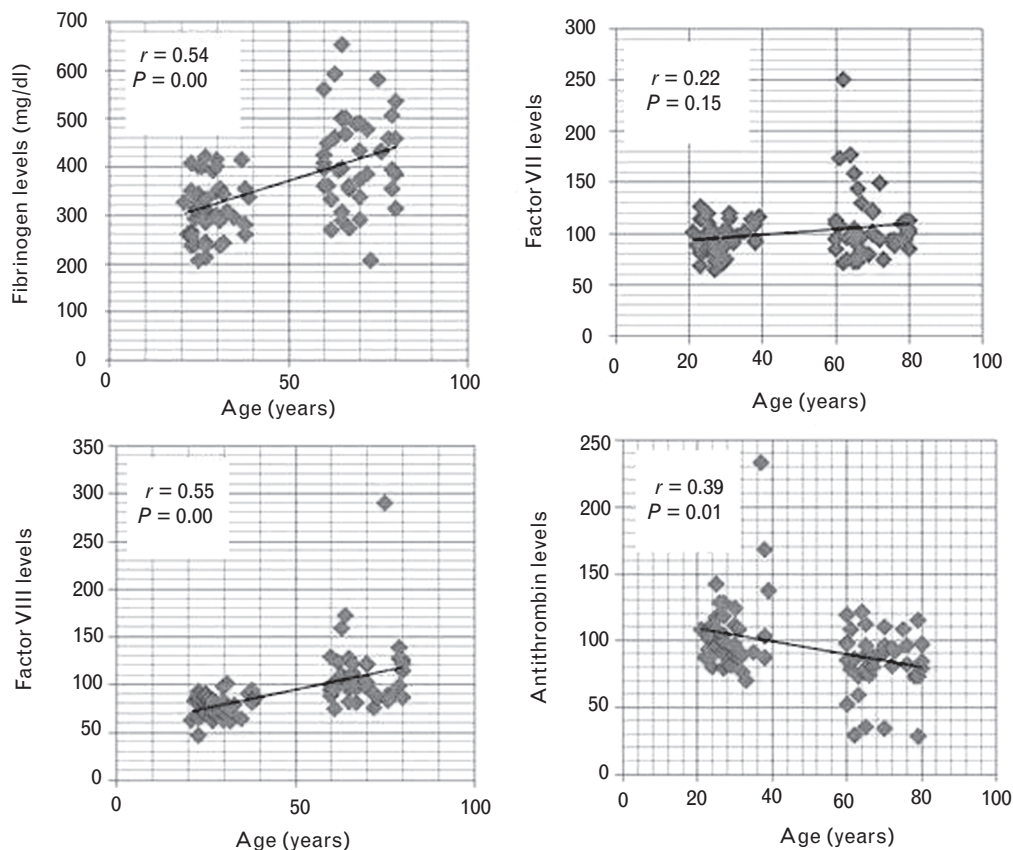
In the present study, we observed increase in fibrinogen level with age ($P=0.001$) which is well supported and consistent with other studies [2,14]. The significant finding was the higher mean levels of fibrinogen in our local healthy population. Considerably, lower levels were noted by Framingham [4] and Miura *et al.* in their studies

Fig. 1



Graphical representation of Pearson's correlation of age (years) with plasma Fibrinogen concentration (mg/dl), factor VII levels (%), factor VIII (%) and plasma antithrombin levels (%) in 46 healthy men. Fibrinogen, factor VII and factor VIII are positively related with age whereas antithrombin is negatively related to age in men.

Fig. 2



Graphical representation of Pearson's correlation of age (years) with plasma fibrinogen concentration (mg/dl), factor VII levels (%), factor VIII (%) and plasma antithrombin levels (%) in 44 healthy women. Fibrinogen, factor VII and factor VIII are positively related with age whereas antithrombin is negatively related to age in women.

[15]. The possible cause of this variation could be that, fibrinogen levels are genetically determined, but life-style and environmental factors influence it [16]. Markovitz *et al.* [17] in their study also showed that Indians had elevated fibrinogen levels relative to the whites. Larger epidemiological studies are needed in our relevant environment to establish the reference ranges and concrete difference in levels of fibrinogen in young and old age.

Another vital finding noted in younger participants was higher mean fibrinogen level in women than men of the young group. Similar results of young women having

higher baseline levels of fibrinogen compared with men were also observed in a study on patients with ischemic heart disease [18].

In our study, we also observed a significant effect of increased age on factor VII percentage activity ($P = 0.05$). These age-related differences in factor VII have been reported elsewhere also [4,19,20]. In our results the magnitude of rise of factor VII level from young to elderly group was much greater in women ($P = 0.03$). This confirmed the previous observation that factor VII activity was only related to age in women [21]. In their study Scarabin *et al.* [22] observed that the magnitude of rise of

Table 4 Correlation of haemostatic variables with age

| Study variable | Combined (men and women) | | Men | | Women | |
|--------------------------|--------------------------|---------|---------|---------|---------|---------|
| | r value | P value | r value | P value | r value | P value |
| Fbg (mg/dl) | 0.54 | 0.00 | 0.54 | 0.00 | 0.54 | 0.00 |
| Factor VII (% activity) | 0.20 | 0.05 | 0.22 | 0.14 | 0.22 | 0.15 |
| Factor VIII (% activity) | 0.55 | 0.00 | 0.55 | 0.00 | 0.55 | 0.00 |
| AT (% activity) | -0.39 | 0.00 | -0.37 | 0.01 | -0.39 | 0.01 |

AT, antithrombin; Fbg, fibrinogen, Combined men and women $n = 90$, men $n = 46$, women $n = 44$.

factor VII levels was significantly greater in women with age. Study conducted earlier showed that young women have lower level of factor VII than young men but opposite to this was observed in men and women of older age group [7]. A study conducted in France showed that factor VII was positively and significantly associated with the menopause [23].

The present study showed that plasma levels of factor VIII in elderly participants particularly presented higher levels as compared to the younger group, which is in agreement with earlier observation [2,24,25]. In our results of factor VIII, we did not observe any noteworthy sex-related differences in both age groups. Observation similar to ours was also made in a study supporting no statistically significant sex difference in factor VIII levels [26].

Our results verified that younger healthy individuals demonstrate significantly higher antithrombin activity, which tends to decrease with age ($P=0.001$). Similar findings were also made by Fagerhol and Abildgaard as cited by Rahman *et al.* [27] and also in other studies [28,29]. It has been reported earlier that younger women have significantly lower concentrations of antithrombin compared with men of the same age [18,30,31]. Meade *et al.* also reported that the occurrence of menopause in women was accompanied with a significant increase in antithrombin levels than their male contemporaries [32]. Failure to elicit these sex-related differences in older age group in our study might be due to the fact that sample selection of elderly women in our study was above 60 years. Menopause happens years before this age and these increased levels of antithrombin fall again later after menopause in older women [33].

It is concluded that significant effects of age and sex occur on commonly measured coagulation factors and coagulation inhibitors. Relatively high fibrinogen levels than other ethnic groups were also observed in our local population. Significant increase in fibrinogen, factor VII, and factor VIII plasma levels were observed with age. It was also found that this increase in factor VII with age was mainly contributed by the female part of the normal population. Younger healthy individuals had higher antithrombin concentration and this tended to decrease significantly with age.

Limitations of study

Only two age groups with wide range of ages (20–40 and 60–80 years) were included in our study, which is insufficient to establish normal values to document the effect of age and sex on haemostatic system in the Pakistani population.

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Conflicts of interest

There are no conflicts of interest.

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