Research Article,

The Coagulation Parameters Among Healthy Menopausal Sudanese Women

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Abstract:

Background:
Menopause is a natural stage in life and part of the aging process. it marks when a woman's period stops as her ovaries stop producing eggs. Many changes take place in the physiological parameters some of which are known to enhance the risk of vascular-related diseases such as stroke and ischemic heart disease. This study aimed to estimate the platelets count, PT, APTT, fibrinogen level D-dimer, and protein C level among Healthy Menopausal Sudanese Women.

Material and methods:
This was a case-control study conducted at the laboratory of the national university at Khartoum state during the period of December 2022 to April 2023. Apparently, healthy menopausal women who lost their menstrual period for more than one year were included as a case group, and apparently healthy women during the reproductive period were included as a control group. The platelets were counted by using Automated Hematology Analyzer, Sysmex KX 21N (series SN B 2010), PT, APTT by coagulometer (Automated Bio Bas), Fibrinogen level by using the coagulometer (Automated Bio Bas) by BioMed-Fibrinogen kite BioMed-Fibrinogen kite, I chroma was used for the D-dimer, protein C was measured by using (URIT 660 AESKULISA Protein C and S Microplate read.

Results:
In the case group the means of platelets count, PT, APTT, Fibrinogen, D-dimer, and Protein C were; (251.3±38.2), (16.9±2.1), (32.9±7.7), (381.0±269.1) (0.59±0.17) and (89.9±16.3) respectively. while in the control group, the means of platelets count, PT, INR, APTT, Fibrinogen, D-dimer, and Protein C were; (291.8±73.5), (13.5±1.5), (31.3±2.7), (212.5±77.3) (0.33±0.12) and (82.2±14.2) also respectively. when comparing the parameters means between the case and control group the results revealed; there was a significant decrease in platelets counts (p. v = 0.001), a significant increase in PT and fibrinogen levels (p. v = 0.000), and insignificant differences for the APTT, D-dimer, and protein C (p. v > 0.05). In addition to that, there was a negative correlation between the parameters and the age and the A menorrhea (p. v > 0.05)

Conclusion:
In the Sudanese menopausal women, there was a significant decrease in platelets counts, and a significant increase in PT and fibrinogen levels, with insignificant differences for the APTT, D-dimer, and protein C when compared between the case and control group, in addition, the parameters had a negative correlation with the age and the A menorrhea.

Introduction:

Menopause is a natural stage in life and part of the aging process. it marks when a woman's period stops as her ovaries stop producing eggs. Many changes take place in the physiological parameters, some of which are known to enhance the risk of vascular-related diseases such as stroke and ischemic heart disease. Such changes may include alterations in fat distribution and metabolism and coagulative and fibrinolytic properties in blood. Endothelial dysfunction along with undesirable alterations in fibrinolysis, coagulation, and other metabolic processes has been known to occur. (1) Some studies have revealed that there is a higher risk of coronary artery disease for women after menopause, especially, if there are coexisting lifestyle factors such as physical inactivity, habits like smoking, high-calorie/high-fat diet, and stress full work conditions.[1,2,3]

Menopause is caused by several factors. But the most common one is natural aging while others are through a hysterectomy, ovarian cancer patients, chemotherapy, pituitary gland disorders, and very poor health condition. Aging comes with the inability of the body to produce estradiol or inhibin, therefore, the follicle-stimulating hormone and luteinizing hormone can no longer be inhibited by estrogen's negative feedback mechanism. Furthermore, with aging leading to menopause, the cyclical production of estradiol and progesterone by the ovaries reduces and becomes inconsistent. These usually occur in the late 40s to early 50s of age but could also occur any time after 35 years of age. [4] According to the published data, Menopause can cause many changes in the body, many symptoms are occurred due to a decreased production of estrogen and progesterone. In Sudan, there is no clear published data regarding the hematological hangs that occur in menopausal women generally, for that this study was designed to count the platelets and measure PT, PTT, fibrinogen, D-dimer, and Protein C levels among the healthy menopausal Sudanese women.

Materials and Methods:

This case-control study was conducted at the laboratory of the national university at Khartoum State from December 2022 to April 2023. Apparently, healthy menopausal women who lost their menstrual period for more than one year were included as a case group, and apparently healthy women during the reproductive period were included as a control group. Participants refuse to give consent, and those with a previous history of bleeding, thrombi, under anticoagulant drugs, or under hormonal therapy were excluded from the study. The study was approved by the ethical committee of the national university, faculty of medical laboratory, and the participants were fully informed about the advantages and disadvantages before participation in the research (verbal informed consent). From each participant, 2.8 ml of blood samples were collected in trisodium citrate anticoagulant containers for PT, PTT, fibrinogen, D-dimer, and Protein C, and 3 ml was collected in the EDTA containers for the platelets count.

The platelets were counted by using Automated Hematology Analyzer, Sysmex KX 21N (series SN B 2010), PT, APTT by coagulometer (Automated Bio Bas), Fibrinogen level was estimated by using the coagulometer (Automated Bio Bas) by BioMed-Fibrinogen kite BioMed-Fibrinogen kite, I chroma was used for the D-dimer, protein C was measured by using (URIT 660 AESKULISA Protein C and S Microplate read

Results:

In the present study total of hundred participants were in roll, fifty as a case group and fifty as a control group. The mean age in the case group was (48.7±5.3) and in the control group was (28.2±6.6). In the case group, the frequency of A menorrhea was; 14% for 7 years, 10% for 5 years, and 6% for years. (figures1,2)
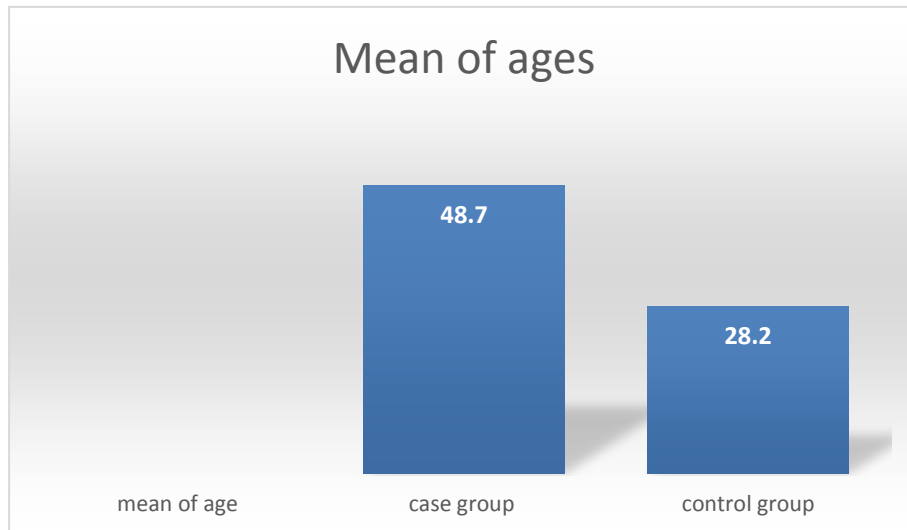
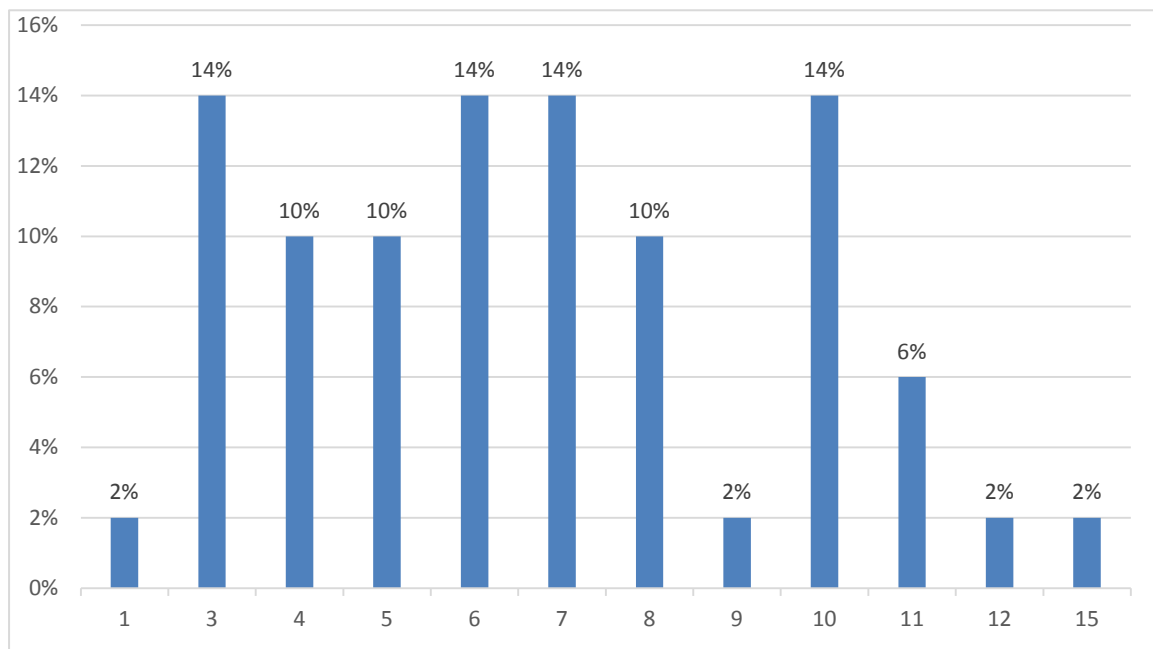**Figure (1) Mean of ages in the case and control group**

Figure (2): Distribution of A menorrhea in the case group

Hematological Results:

The results of this study showed; in the case group the means of platelets count, PT, APTT, Fibrinogen, D-dimer, and Protein C were; (251.3±38.2), (16.9±2.1), (32.9±7.7), (381.0±269.1) (0.59±0.17) and (89.9±16.3) respectively. while in the control group, the means of platelets count, PT, INR, APTT, Fibrinogen, D-dimer, and Protein C were; (291.8±73.5), (13.5±1.5), (31.3±2.7), (212.5±77.3) (0.33±0.12) and (82.2±14.2) also respectively. when comparing the parameters means between the case and control group the results revealed; there was a significant decrease in platelets counts (p. v = 0.001), a significant increase in PT and fibrinogen levels (p. v = 0.000), and insignificant differences for the APTT, D-dimer, and protein C (p. v > 0.05) (table 1). In addition to that, there was a negative correlation between the parameters and the age and the A menorrhea (p. v > 0.05) (table 2,3)

Table (1): Comparison of protein C, PT, APTT, platelet, fibrinogen, and D-dimer between case and control

Parameters	Study population		P. value
	Case	Control	
Protein C	89.9 ± 16.3	82.2 ± 14.2	0.080
PT	16.9 ± 2.1	13.5 ± 1.5	0.000*
APTT	32.9 ± 7.7	31.3 ± 2.7	0.140
Platelet	251.3 ± 38.2	291.8 ± 73.5	0.001*
Fibrinogen	381.0 ± 269.1	212.5 ± 77.3	0.000*
D-dimer	0.59 ± 0.17	0.33 ± 0.12	0.117

Table (2): Correlations of age with protein C, PT, APTT, platelet, fibrinogen, and D-dimer

	Age (years)	
	Pearson Correlation	P. value
Protein C	-.137	.515
PT	-.035	.810
INR	-.062	.669
APTT	.054	.710
Platelet	.015	.918
Fibrinogen	.028	.847
D-dimer	-.018	.903

Table (3): Correlations of A menorrhea with protein C, PT, APTT, platelet, fibrinogen, and D-dimer

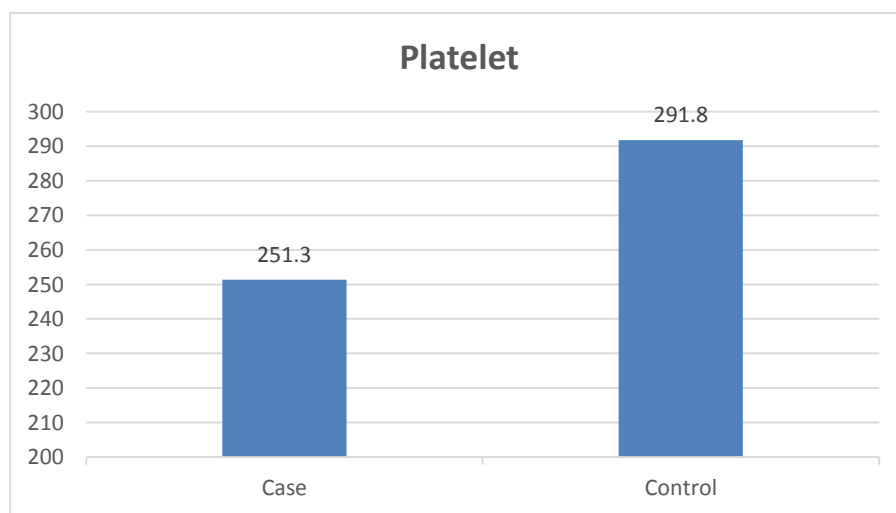|	Period interruption (years)	
	Pearson Correlation	P. value
Protein C	.106	.615
PT	-.182	.205
INR	-.216	.132
APTT	-.162	.260
Platelet	.033	.822
Fibrinogen	-.186	.197
D-dimer	.272	.056

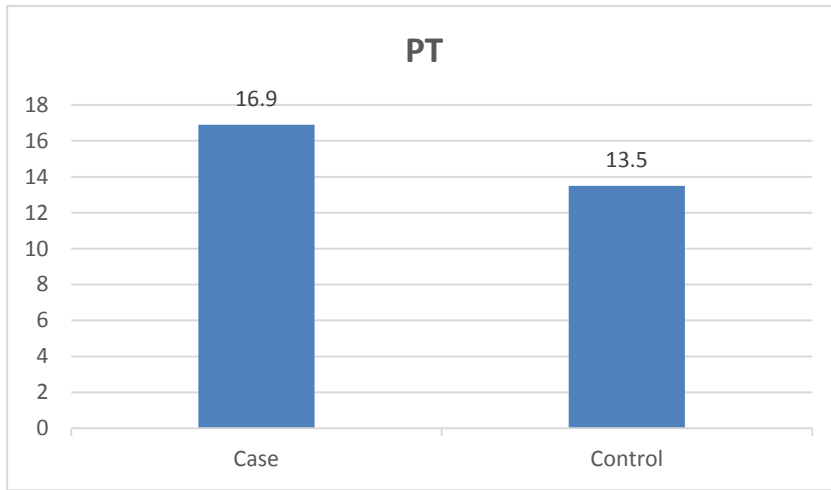**Figure (3): Mean of platelet in case and control**

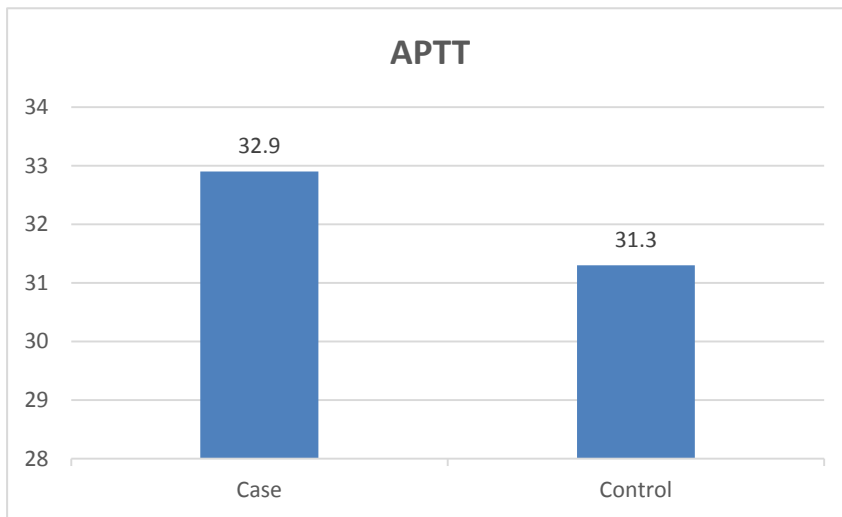**Figure (4): Mean of PT in case and control**

Figure (5): Mean of APTT in case and control
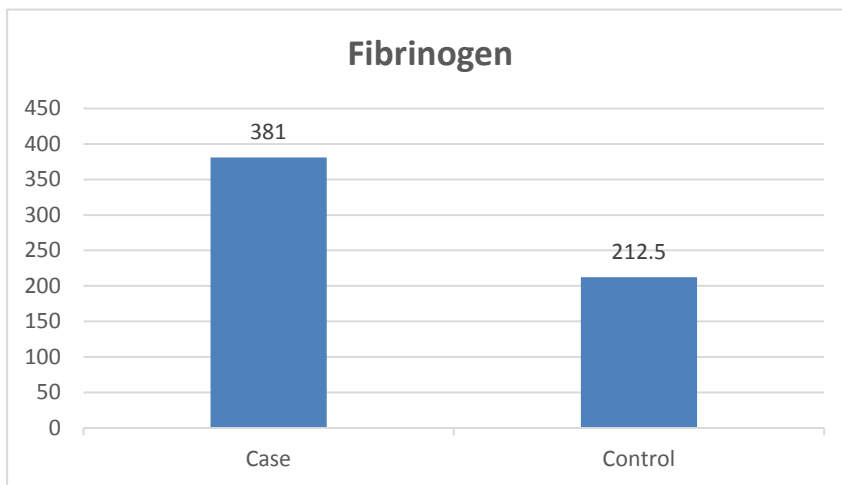

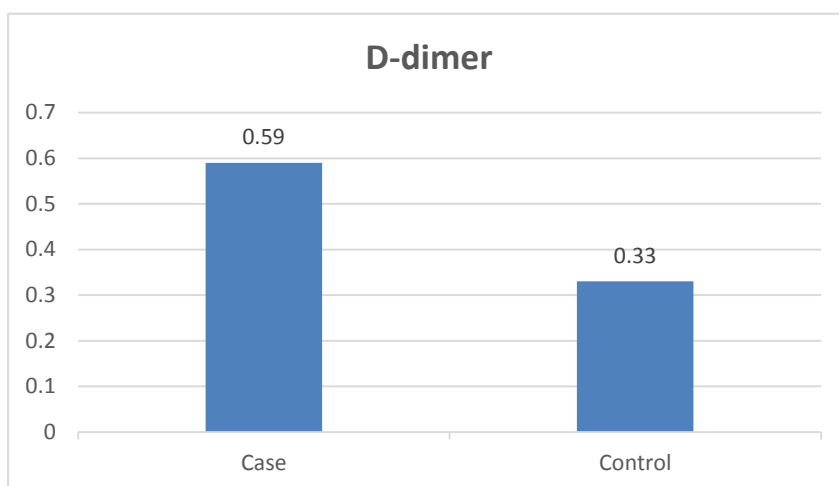**Figure (6): Mean of fibrinogen in case and control**

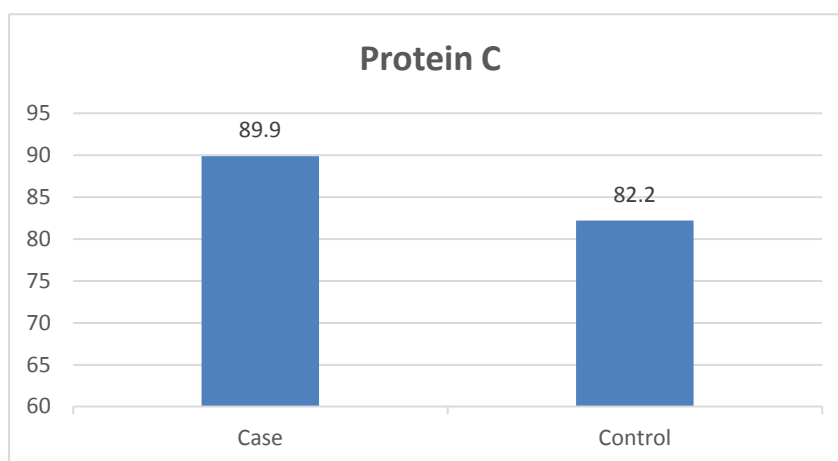**Figure (7): Mean of D-dimer in case and control**

Figure (8): Mean of protein C in case and control

Discussion:

Medical professionals often define menopause as having occurred when a woman has not had any menstrual bleeding for a year. It may also be defined by a decrease in hormone production by the ovaries. [1]. This was a case-control study conducted at the laboratory of the national university at Khartoum state during the period of December 2022 to April 2023 and aimed to estimate the Platelets count, Prothrombin Time, and Activated Partial Thromboplastin Time, fibrinogen level, D-dimer and protein C level among healthy menopausal Sudanese women, the results showed that; the mean of ages in the case group was (48.7±5.3), the frequency of A menorrhea was; 14% for 7 years, 10% for 5 years and 6% for years.

Takahashi et al reported; Menopause typically occurs at some point between 47 and 54 years of age. According to various data, more than 95% of women have their last period between the ages of 44–56 (median 49–50). 2% of women under the age of 40, 5% between the ages of 40–45, and the same number between the ages of 55–58 have their last bleeding. [5] Also, Ringa et al mentioned the average age of the last period in the United States is 51 years, in Russia is 50 years, in Greece is 49 years, in Turkey is 47 years, in Egypt is 47 years and in India is 46 years The menopausal transition or perimenopause leading up to menopause usually lasts 3–4 years (sometimes as long as 5–14 years). [6]

In the present study the means of platelets count, PT, and APTT, were; (251.3±38.2), (16.9±2.1), (32.9±7.7) respectively. While in the control group, the means of platelets count, PT, and APT were; (291.8±73.5), (13.5±1.5), (31.3±2.7) also respectively. when comparing the parameters

means between the case and control group the results revealed; there was a significant decrease in platelets counts (p. v = 0.001), a significant increase of PT (p. v = 0.000), and insignificant differences for the APTT (p. v > 0.05). Also, there was a negative correlation between the parameters, the age, and the A menorrhea. This finding consists of the Anjali et al results which reported; The platelet count is decreased in 60% of subjects, the increased ESR and decreased platelet count in the menopausal group appear to be a significant alteration and need further study. Estimation of fibrinogen content of blood along with Bleeding time and Clotting time, female sex hormones in the menopausal age group will definitely guide to the explanation. [7] Achie et al said, decreasing platelet counts explain the cause of increased bleeding tendencies in the menopausal age group. However, the decreased platelet count may be due to decreased marrow activity with age or an effect of decreasing hormones with the age. Oestrogen hormone has been implicated as an indicator of erythropoiesis. However, some of the studies showed a rise in hematological parameters. [8] Butkiewicz et al revealed that; Lower platelet count in a woman after menopause than in young women probably was a result of a decreased concentration of estrogens. A higher percentage of reticulated platelet in the group of woman after menopause than in the group before menopause suggests that it is a more sensitive parameter of thrombocytopoiesis than others. Higher beta-thromboglobulin level confirms platelet activation in postmenopausal women. [9]

In the present study, there was a significant increase in PT, and insignificant differences for the APTT, this results disagreed with Ebengho et al study which found; PTT was significantly lower and the PT was not significantly different between the study groups, relative plasma viscosity correlated positively with age. These changes may be due to age or a decline in circulating oestrogen levels [10]. Also, Schneider et al showed; significantly lower PTT without a concurrent change in PT or plasma fibrinogen concentration implies that the coagulation factor(s) of coagulation responsible for this belongs to the intrinsic coagulation pathway. [11] Previous authors reported significantly higher hematocrit and lower platelet count, a significantly lower APTT, PT, and International Normalized Ratio (INR). This observation is not

consistent in some ways with the findings from the present study. The authors suggested that the higher values for PCV may enhance red blood cell aggregation, and the raised viscosity might aggravate the atherosclerotic risk. Elevated platelet count may increase the adhesiveness of platelets to the subendothelium tissues, and higher leakage of proteins through the vessel wall may increase atherosclerotic risk. [12]

In this study, The mean of Fibrinogen was (381.0±269.1) in the case group, while in the control group was (212.5±77.3), when compared the fibrinogen means between the case and control group there was a significant increase (p. v = 0.000). In addition to that, there was a negative correlation between the fibrinogen, the age, and the A menorrhea. These results disagreed with Meilahn et al results which reported; low plasma concentrations of fibrinogen were found among women aged 49 to 55, selected hemostatic measures varied (within normal ranges) by menopausal status, and were altered by HRT. [13] Also, Qin Yu et al found that; the level of fibrinogen in the menopausal group was significantly lower than the postmenopausal group.

However, these results agreed with El Khoudary et al study which found; C3 was associated with higher levels of log PAI-1 and tPA-ag, while C4 was associated with higher levels of log factor VIIc and fibrinogen in menopausal women. C3 and C4 may be related to blood clots via their associations with hemostatic markers and C3 is related to menopausal status. [14,15] In addition, DeSouza et al found that Plasma fibrinogen levels were -15% lower (p = .001) in the physically active women (2.48 ± .08 g/L) than the sedentary controls (2.92 ± .06 g/L) and -7% lower (p = .04) in the users (2.65 ± .08 g/L) versus nonusers (2.84 ±.08 g/L) of HRT. Moreover, the lower (0.4 g/L) plasma fibrinogen levels associated with regular physical activity were evident in both the users (2.39 ±.11 vs 2.80 ± .08 g/L, p = .001) and nonusers (2.56 ±.11 vs 3.03 ± .08 g/L, p = .006) of HRT. Stepwise multiple regression analysis revealed that percent body fat was the primary determinant of plasma fibrinogen levels, accounting for 30% of the variability. [16] Bucciarelli et al steady; The process of aging is accompanied by several modifications in the hemostatic system at different levels (blood coagulation, fibrinolysis, platelet activity, vascular endothelium). These changes may explain the

higher incidence of arterial and venous thrombosis in the elderly compared to young people. Genetic and environmental factors modulate in different combinations the expression of proteins involved in the hemostatic process. Among the latter, diet and smoking habits play an important role, as well as physical exercise and, for women, hormonal status. No laboratory parameters of hemostasis are predictive of thrombosis on an individual basis, a physician's behavior towards aging patients (e.g. prescription of hormonal replacement therapy to a woman during menopause) should not be affected by laboratory tests, but mainly by a patient's clinical history and the presence of strong risk factors for thrombosis other than age. [17] Chen et al reported that; higher fibrinogen levels were associated with lower bone mineral density in menopausal women, which was independent of age, body mass index, estradiol, and other factors. Therefore, serum fibrinogen can be used as a new predictor of reduced bone mineral density (BMD in menopausal women. [18]

Regarding the D- dimer results in the present study there are insignificant differences between the case and control group, this finding disagreed with Cushman et al which revealed; lower protein C and free protein S, and higher D-dimer, prothrombin fragment 1.2 and plasmin-ant plasmin complex were associated with risk of future thrombosis in the menopausal women. Abnormal levels of biomarkers of thrombosis risk identified women at increased risk of future venous thrombosis with oral menopausal hormone therapy. Findings support the potential for clinical use of D-dimer testing in advance of hormone therapy prescription. [19]

However, AL-DEJALY et al reported; There is a significant reduction in serum D-dimer levels in menopausal women with IHD. Diabetes mellitus and hypertension are associated with a significant increase in serum D-dimer levels in menopausal women with IHD. Serum D-dimer can be used as a biomarker for the diagnosis of angina and AMI in menopausal women. Both DM and hypertension have detrimental effects on serum D-dimer levels. [20]

Koh et al mentioned clear relation between the activation of the coagulation system and hormone replacement therapy (HRT) they said; activation of coagulation pathways has been detected in postmenopausal women treated with HRT in the observational and clinical studies. HRT has been shown to enhance systemic fibrinolysis with decreased plasma plasminogen activator inhibitor-1 (PAI-1) levels. In addition, levels of D-dimer exhibited a significant inverse correlation with PAI-1 levels, suggesting enhanced fibrinolysis potential. Activation of coagulation following HRT may not be balanced by activation of fibrinolysis in some postmenopausal women [21]

Menopausal hormone therapy (MHT) containing estrogens increases the risk of deep vein thrombosis (DVT) and pulmonary embolus (PE). The thrombotic effects of MHT containing oral oestrogen are associated with a slightly increased risk of stroke and venous thrombiembolism (VTE) but not of coronary heart disease. [22,23]

Finally, In the present study, the mean of Protein C was (89.9±16.3), in the control group was (82.2±14.2). when comparing the Protein C means between the case and control group there were insignificant differences (p. v > 0.05), also there was a negative correlation between protein C, age, and A menorrhea. This finding disagreed with Robert Campbell etal study which reported; protein C activity displays a log-normal distribution and significant variation with age. This is most marked in young adult males when mean PC activity rises from 0.86 iu/ml (15–19 years) to 1.04 iu/ml (45–49 years; P <0.0001). Pre-menopausal females, who for most age ranges, have mean PC activity below their male contemporaries, show a less marked rise with age until menopause when PC activity rises further. The use of hormonal contraceptive preparations is associated with an increase in mean PC activity of 0.05–0.08 iu/ml while the smoking habit has no influence on PC activity. [24] another study showed that; In females, increasing age was associated with a rise in AT, PC, and PS plasma levels mainly in the menopause state [25] Furthermore, Cushman et al revealed; lower protein C and free protein S, and higher D-dimer, prothrombin fragment 1.2 and plasmin-ant plasmin complex were associated with risk of future thrombosis in the menopausal women. Abnormal levels of biomarkers of thrombosis risk identified women at increased risk of future venous thrombosis with oral menopausal hormone therapy. Findings support the potential for clinical use of D-dimer testing in advance of hormone therapy prescription. [26] However Cushman et al found; HRT-induced alterations in anticoagulant function in relation to the occurrence of thrombosis, Venous thrombosis from HRT may be

mediated partly by alterations in antithrombin, but not protein C concentrations. [27]

Conclusion:

In the Sudanese menopausal women, there was a significant decrease in platelets counts, and a significant increase in PT and fibrinogen levels, with insignificant differences for the APTT, D-dimer, and protein C when compared between the case and control group, in addition, the parameters had a negative correlation with the age and the A menorrhea.

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