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Hormonal replacement therapy is associated with a higher risk of inflammatory and bleeding disorders

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SUMMARY

AUTHORS' CONTRIBUTION: (A) Study Design · **(B)** Data Collection. **(C)** Statistical Analysis · **(D)** Data Interpretation · **(E)** Manuscript Preparation · **(F)** Literature Search · **(G)** Funds Collection

Background: Various biochemical markers levels rise with postmenopausal Hormone Replacement Treatment (HRT). Inflammatory indicators like CRP promote cardiovascular problems. However, the therapeutic ramifications of HRT-induced CRP alterations are unclear.

Methods: A study was conducted between January 2000 and February 2023 to investigate the association between inflammatory markers, thrombosis, and coronary heart disease. The study cohort comprised 608 individuals who were free of cardiovascular disease and cancer at the time of baseline assessment. Participants were surveyed on their utilization of hormone therapy, which was categorized into three groups: 'non-user,' 'E' (estrogen-only therapy), and 'EP' (estrogen-progestin therapy). Further subgroup analyses were conducted within these categories.

Results: In the study, 83% of women on E had undergone hysterectomy, with a median duration of estrogen use of 16.5 years. This is in comparison to the shorter duration of estrogen use for EP users, 96% of whom had undergone hysterectomies. The number of estrogen use cases (140) nearly doubled those of EP (70). Furthermore, a higher prevalence of diabetes history was observed in non-PHT users (12%) compared to E (3.7%) and EP users (2.8%). Finally, non-users exhibited a higher incidence of coronary events (56.5%) compared to E (45.5%) and EP users (45.1%). CRP levels were significantly higher in PHT users, especially female E users, even after adjustments. E users showed a significant decrease in tPA-antigen ($p < 0.05$), while IL-6 and sICAM-1 were reduced in EP users but not E users, though these differences disappeared in multivariate models. D-dimer levels remained the same. HDL and triglyceride levels were higher in PHT users, particularly E users, while LDL levels were lower in E users.

Conclusion: The study revealed significant differences in biomarkers between CEE users and non-users. CEE users exhibited lower sICAM-1 and higher tPA-antigen, homocysteine, and HDL levels, while IL-6, sICAM-1, D-dimer, total cholesterol, and LDL levels remained unchanged. Of particular interest was the observation that sICAM-1 levels were markedly lower in CEE users who also used P, contrasting with the higher levels seen in CEE-alone and non-CEE EP users.

Keywords: CRP; Estrogen; Progesterone; HRT; Inflammatory; Bleeding

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INTRODUCTION

Numerous soluble inflammatory markers have been shown to be negatively modulated by menopausal hormone therapy, which includes different estrogen formulations with or without progestin. These include monocyte chemoattractant protein-1, vascular cell adhesion molecule-1, intercellular adhesion molecule-1, tumor necrosis factor-α, and E-selectin. Furthermore, transforming growth factor-β, a cytokine that protects against blood vessel damage, has been demonstrated to be activated, although the effects on interleukin-6 have been found to be inconsistent [1]. Hormone Replacement Therapy (HRT) in postmenopausal women has been demonstrated to elevate C-Reactive Protein (CRP) levels. Various inflammatory biomarkers, including CRP, have been associated with an increased risk of cardiovascular complications. However, the clinical implications of HRT-induced changes in CRP remain to be fully elucidated [2].

It is important to note that women remain at an elevated risk of experiencing abnormal withdrawal bleeding while undergoing hormone replacement therapy. This is in contrast to endometrial polyps, which do not pose an increased risk of bleeding. It has been established that conducting a hysteroscopic evaluation of the uterine cavity, followed by counselling regarding the potential for heavy or extended bleeding, will assist in their future management and may enhance compliance [3,4]. Hormonal Intrauterine Devices (IUDs), which have seen a surge in popularity following the introduction of Mirena® in 2001 [5], consist of polydimethylsiloxane for controlled release and 52 mg of levonorgestrel in a T-shaped form. This non-abortive technique works by stopping conception and lasts for at least five years [6,7].

The increasing utilization of hormone replacement therapy among women emphasizes the need for a systematic evaluation, as do their possible effects on the cardiovascular system. This study's goal is to compile data regarding the possible oral symptoms that this hormone replacement therapy may cause in women of increase inflammatory and cardiovascular events.

MATERIALS AND METHODS

Method: A cross-sectional study was approved by the Department of Obstetrics and Gynecology at the University of Kufa (No. BORS-Gynecological Science, Res/KU/15-10, 2000-79). The study was conducted from January 2000 to February 2023, with the objective of investigating the association between inflammatory markers and thrombosis with the incidence of coronary heart disease. The study population comprised 608

participants who were free of cardiovascular disease and cancer at the time of the study's inception. Cases and controls were meticulously selected from this large cohort.

We used a questionnaire to ask people about their experience of hormone therapy. First, we asked them if they had ever used hormone therapy after the menopause. Then, we asked them to say if they were still using it, and if they were using pills or patches. After that, we divided the people into three groups. The first group was called 'non-user'. The second group was called 'E', which means 'estrogen-only therapy'. The third group was called 'EP', which means 'estrogen-progestin therapy'. We used these groups to compare the people. We also looked at smaller groups within these categories.

The samples of blood that had been collected from the patients when they were fasting were thawed and tested for various substances in the blood.

Statistics

In order to assess mean differences, the Student's t-test was employed for two-group comparisons and ANOVA for comparisons involving more than two groups. The χ^2 statistic was used to evaluate differences in proportions, while Spearman's correlation coefficients were used to assess univariate associations between biomarkers. One-way ANOVA was used to compare biomarker means by PHT status in all participants, and separately for cases and controls. Variables that were found to be skewed were transformed using the log-transformation function in order to ensure that they were suitable for parametric testing.

RESULTS

Basic clinical characteristics

Of the 608 women included in the study, 210 (34.5%) reported the use of some form of PHT at the time of entry (See **Tab. 1.**). Amongst women on E, it was noted that 83% had undergone hysterectomy, and the median duration of estrogen use was recorded as 16.5 years. In contrast, the median duration of estrogen use was considerably less for women on EP, with 96 percent of these women having undergone hysterectomy.

The prevalence of Estrogen use was found to be nearly double that of Estrogen plus Progesterone, with 140 and 70 cases, respectively. Furthermore, a history of diabetes was reported by nearly 12% of women not taking PHT, compared with 3.7 and 2.8 % among women on E and EP, respectively.

It was observed that non-users exhibited a higher propensity for experiencing an incident coronary event (56.5%) when compared to users of E (45.5%) or EP (45.1%).

A comparison of risk factor levels according to PHT utilization category

Tab. 2. presents the mean baseline values for each biomarker, categorized according to PHT usage. The data demonstrate a statistically significant increase in CRP levels in PHT users compared to non-users, with the highest levels observed among female users of E. This discrepancy remained consistent after adjustment for potential confounders. The study revealed a significant decrease in tPA-antigen levels among E users ($p < 0.05$), which differed significantly from the levels observed in non-users. Furthermore, compared to non-users, IL-6 and sICAM-1 levels were lower in EP users but not in E users. However, when multivariate models were adjusted, these disparities vanished. D-dimer levels remained unchanged between PHT users and non-users. HDL and triglycerides were greater among PHT users, with the highest connection reported in users of E alone. E users had reduced LDL values (**Fig. 1.**).

Tab. 1. The baseline characteristics of the study population in relation to their use of postmenopausal hormone therapy.

Parameters	Non-Users (n=398, 65.5%)	Estrogen Alone (n=140, 23.0%)	Estrogen plus Progestin (n=70, 11.5%)	P value	Significant
Mean age, years (SD)	69.9 (6.1)	68.6 (7.2)	65.6 (6.6)	0.082	No
History of Hysterectomy, %	35.2	83*	4*	0.001	Yes
duration, years	NA	16.5%	6.0	0.001	Yes
History of diabetes, %	10.5	3.3*	2.9*	0.001	Yes
*: vs Non-Users					

Tab. 2. The average level of biomarkers for women who have had hormone therapy after the menopause.

Parameters ± SD	Non-Users (n=398, 65.5%)	Estrogen Alone (n=140, 23.0%)	Estrogen plus Progestin (n=70, 11.5%)	P value	Significant
C-reactive protein (mg/dl)	0.22 ± 0.01	0.38 ± 0.01*	0.33 ± 0.01*	0.002	Yes
Interleukin-6 (pg /ml)	1.75 ± 0.05	1.61 ± 0.03	1.60 ± 1.00	0.095	No
sICAM-1 (ng /ml)	276.2 ± 4.01	274.6 ± 6.06	266.2 ± 6.21	0.064	No
Tissue Plasminogen Activator (ng /ml)	8.5 ± 0.04	6.4 ± 0.06*	6.5 ± 0.29*	0.001	Yes
D-dimer (ng / ml)	25.5 ± 0.01	25.5 ± 0.02	24.5 ± 1.24	0.164	No
Total Cholesterol (mg /dL)	218.0 ± 1.9	220.0 ± 1.5	219.0 ± 1.9	0.079	No
LDL Cholesterol (mg /dL)	126.9 ± 1.5	113.2 ± 1.1*	122.9 ± 1.4	0.001	Yes
HDL Cholesterol (mg / dL)	58.7 ± 1.7	88.2 ± 1.8*	78.5 ± 0.4*	0.001	Yes
Triglycerides (mg /dL)	128.3 ± 6.7	168.2 ± 6.3*	163.5 ± 4.4*	0.001	Yes

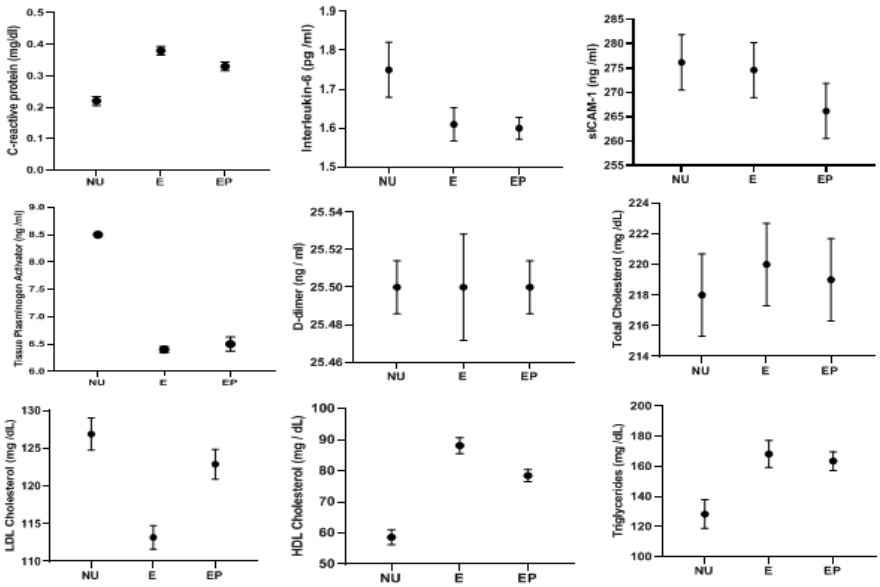

Fig. 1. Average level of biomarkers for people who have had hormone therapy after the menopause.

DISCUSSION

In this cross-sectional investigation, the levels of tissue Plasminogen Activator (tPA)-antigen and C-Reactive Protein (CRP) were examined between patients who used and did not use PHT. The findings showed that, while tPA-antigen and homocysteine levels were lower in PHT users than in non-users, CRP concentrations were higher in women taking the medication. The investigation also revealed significant variations in lipid levels, with PHT users exhibiting lower LDL concentrations and greater HDL and triglyceride values. Furthermore, exploratory analysis identified case-control differences in certain risk factors that were not apparent in comparisons by PHT use category.

In the study, it was observed that women who used CEE exhibited higher CRP levels in comparison to those who were not using CEE or other estrogens. This finding was corroborated by subsequent research in two additional cohorts, which demonstrated an association between elevated CRP levels and PHT use. The study by Cushman, et al. [8] revealed a significant interaction between BMI and CRP levels in users of EP. Specifically, they observed that as BMI increased, CRP levels also increased, suggesting a potential link between BMI and CRP levels. However, this interaction was not observed in users of E. This finding is corroborated by our study's observation that, when accounting for confounding variables such as BMI, the progestin-associated disparity in CRP levels among CEE users becomes negligible. While the association between PHT usage, CRP, and cardiovascular events was not evaluated in this study, baseline CRP levels in women without known disease were found to be associated with subsequent cardiovascular events in the second cohort [9,10]. A significant association between CRP level and case status was identified in both PHT users and non-users, after adjusting for BMI, age, diabetes, and hysterectomy. CRP levels were higher among CEE users in the cohort under investigation, despite the absence of a case-control difference in CRP between women taking CEE and those taking other supplements. A preliminary clinical study involving 19 women suggests that the increase in CRP observed in CEE users may not be attributable to transdermal estradiol use [4,11], whereas a minor clinical trial of oral estradiol showed an increase in CRP [12]. The latter finding is supported by our transdermal estrogen results. Given the established role of CRP as a predictor of coronary events, the differential impact of CEE and non-CEE PHT on CRP elevation warrants further investigation.

IL-6 levels in PHT users have been found to be both lower [13,14] and higher [15,16] in other investigations. The present study revealed no significant differences in D-dimer levels between patients treated with PHT and those not receiving the treatment. However, the investigation did identify a notable case-control disparity in IL-6 levels, which was exclusively observed among patients undergoing EP. The absence of substantial variation in IL-6 is particularly noteworthy in the context of the observed disparities in CRP, given IL-6's regulatory role in CRP synthesis. These findings imply that CRP levels are potentially influenced by additional factors, some of which may be modulated by specific PHT components. The investigation revealed no significant variation in D-dimer levels based on PHT usage. Previous clinical trials of PHT have demonstrated elevated D-dimer levels [17,18], whereas investigations conducted on long-term users have typically not revealed any differences or indicated a drop [19,20]. Our data is consistent with the latter and represents long-term use. Higher D-dimer levels were linked to case status in both women who used EP and non-users, even though there was no overall difference in D-dimer levels between PHT users and non-users in the current study.

CONCLUSION

The present study has identified significant differences in the levels of certain biomarkers between patients who use CEE and those who do not. Specifically, lower levels of sICAM-1 and higher levels of tPA-antigen, homocysteine, and HDL were observed in the CEE user group. However, no significant differences were observed in the levels of IL-6, sICAM-1, D-dimer, total cholesterol, and LDL between the two groups. The finding of substantially lower levels of sICAM-1 only in users of CEE with P is surprising, especially since levels were much higher in users of CEE alone and users of non-CEE EP.

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