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Hormone replacement therapy and serum uric acid in postmenopausal women: A cardiometabolic insight

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ABSTRACT

Background and aims: Elevated serum uric acid (SUA) is an independent marker of cardiometabolic risk in postmenopausal women. Hormone replacement therapy (HRT) may influence SUA levels, though mechanisms and clinical implications remain underexplored. This study compares SUA and cardiometabolic indicators in HRT users and nonusers within a cardiovascular prevention cohort.

Methods and results: We conducted a cross-sectional analysis of 440 postmenopausal women attending a cardiovascular prevention clinic. Participants were stratified by HRT use (n = 109 users vs. n = 331 nonusers). Clinical, biochemical, and lifestyle data were collected. SUA and lipid profiles were compared using t-tests with significance set at $p < 0.05$.

HRT users had significantly lower SUA (5.4 ± 0.27 mg/dL) versus nonusers (6.6 ± 0.24 mg/dL, $p < 0.001$), along with reduced LDL cholesterol, BMI, and waist circumference. No renal function differences were observed.

Conclusions: HRT use is associated with lower SUA and more favorable cardiometabolic profiles in postmenopausal women. HRT may play a protective metabolic role and could support tailored cardiometabolic prevention in postmenopausal women.

1. Introduction

Uric acid has emerged as a relevant metabolic and cardiovascular biomarker, especially in postmenopausal women [1,2]. Elevated SUA levels are associated with hypertension, insulin resistance, and cardiovascular events [1,2]. Hormone replacement therapy (HRT) may modulate urate metabolism via renal clearance and hormonal regulation [3]. Prior studies, including a 12-month follow-up by Sumino et al., observed SUA reductions in hyperuricemic HRT users [4]. In the Third National Health and Nutrition Examination Survey Menopause was associated with higher serum uric acid (SUA) levels. After adjusting for covariates, serum uric acid levels among women with natural menopause and surgical menopause were greater than premenopausal women by 0.34 mg/dl (95 % confidence interval [CI], 0.19 to 0.49) and 0.36 mg/dl (95 % CI, 0.14 to 0.57), respectively [5]. Authors found that postmenopausal hormone use was associated with a lower SUA level among postmenopausal women (multivariate difference, 0.24 mg/dl [95 % CI, 0.11 to 0.36].

However, in recent years several changes have been observed in HRT both in terms of the start of therapy, the combination of hormones and finally the duration of the same [6]. All these factors could have modified the metabolic response of the woman. The aim of the present study was to evaluated the metabolic parameters in relation to hormone replacement therapy in a homogeneous population of women followed for a long time.

This study compares SUA and cardiometabolic indicators in HRT users and nonusers within a cardiovascular prevention cohort.

2. Methods

We enrolled 440 postmenopausal women (mean age 58 ± 6 years). Patients were refereed to our clinic from general practitioners for

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screening and prevention of CVD. We selected women only if they were free of symptoms of Peripheral Arterial disease and had ankle brachial index (ABI) evaluation. Demographic data, clinical characteristics of patients and methods of data collection and ABI measurement have been previously published [7,8] In this retrospective analysis women were categorized as current HRT users (n = 109) or nonusers (n = 331). Regimens included oral combined HRT (estrogen and progestogen), skin patches combined HRT, and other formulations. Data included fasting labs (SUA, LDL, creatinine), BMI, waist circumference, nutritional habits and physical activity (questionnaire-based) [5]. Additional variables collected included age at last visit, age of menopause, and the duration of HRT use. For the purpose of cardiovascular risk stratification, we also evaluated the proportion of women with serum uric acid (SUA) > 5.26 mg/dL, a threshold previously shown to be significantly associated with an increased risk of myocardial infarction in women but not in men [9]. SUA was measured using enzymatic uricase-peroxidase method. Data were collected during the last visit between September 2024 and May 2025. Group comparisons were made using independent t-tests or chi-square tests as appropriate. This study was approved by the Ethics Committee of Area Vasta … …. [hidden for review] approval number 0009960/19. All participants signed an informed consent.

3. Results

Table 1 provides a comparative analysis of clinical, metabolic, lifestyle, and cardiovascular risk variables between postmenopausal women using hormonal replacement therapy (HRT, n = 109) and those not using HRT (non-HRT, n = 331). Mean age and age at menopause were comparable between groups, and the mean duration of HRT use in current users was 30 ± 13 months.

Women in the HRT group had significantly lower serum uric acid levels (5.4 ± 0.27 mg/dL versus 6.6 ± 0.24 mg/dL; p < 0.001) and LDL cholesterol (114.1 ± 30.4 vs. 122.5 ± 27.8 mg/dL; p < 0.001), as well as lower body mass index (BMI) and waist circumference (both p < 0.01). When applying the prognostic cutoff of 5.26 mg/dL identified by the URRAH study, 52.3 % of HRT users and 64.0 % of nonusers exceeded this threshold (p < 0.05).

Serum creatinine levels were within the normal range and similar between groups, excluding renal clearance bias. Importantly, after normalization for creatinine, the SUA/SCr ratio remained significantly lower in HRT users (5.4 ± 0.3) compared with nonusers (7.6 ± 0.4, p < 0.001), indicating that the observed differences are not explained solely by renal function.

No significant differences were found in adherence to the Mediterranean diet. However, women in the HRT group had a lower prevalence of sedentary lifestyle (70.6 % vs. 76.7 %, p = 0.05) and a significantly higher proportion engaged in high levels of physical activity (22 % vs. 9.3 %, p = 0.01). Regarding cardiovascular risk factors, the HRT group showed a lower prevalence of hypertension (36.7 % vs. 53.1 %, p = 0.01), diabetes or prediabetes (20.2 % vs. 29.6 %, p = 0.05), and dyslipidemia (33.0 % vs. 50.4 %, p = 0.001).

Table 1
Clinical and Biochemical Characteristics of HRT vs. Non-HRT Users.

Variable	HRT Group (n = 109)	Non-HRT Group (n = 331)	p-value
Age at last visit (years)	57 ± 1.5	59 ± 3	n.s.
Age at menopause (years)	54 ± 1.3	55 ± 2.6	n.s.
Serum Uric Acid (mg/dL)	5.4 ± 0.27	6.6 ± 0.24	<0.001
LDL Cholesterol (mg/dL)	114.1 ± 30.4	122.5 ± 27.8	<0.001
Creatinine (mg/dL)	1.0 ± 0.17	0.9 ± 0.23	n.s.
SUA/SCr ratio	5.4 ± 0.3	7.6 ± 0.4	<0.001
BMI (kg/m^2)	24.3 ± 2.2	27.6 ± 3.1	<0.01
Waist Circumference (cm)	88.6 ± 21.0	92.3 ± 24.1	<0.01
Adherence to Med D (MedD score)	32.3 ± 2.4	29.9 ± 3.1	n.s.
Vegan Nr of subjects and (%)	3 (2.7)	14 (4.2)	n.s.
Vegetarian Nr of subjects and (%)	11 (10.0)	40 (12.0)	n.s.
Sedentary lifestyle Nr of subjects and (%)	77 (70.6)	254 (76.7)	0.05
High level of physical activities Nr of subjects and (%)	24 (22)	31 (9.3)	0.01
Cardiovascular risk factors			
Hypertension Nr of subjects and (%)	40 (36.7)	176 (53.1)	0.01
Diabetes and prediabetes Nr of subjects and (%)	22 (20.2)	98 (29.6)	0.05
Dyslipidemia Nr of subjects and (%)	36 (33.0)	167 (50.4)	0.001

4. Discussion

These results suggest that HRT use is linked to lower SUA levels and favorable cardiometabolic parameters in postmenopausal women. The mechanism linking HRT use to lower SUA levels is likely multifactorial. Estrogens may enhance renal uric acid clearance, but our findings show that differences remain significant even after normalization for renal function, suggesting that additional pathways are involved. Hormonal modulation of inflammatory responses, endothelial function, and insulin sensitivity may also contribute to the favorable metabolic profile observed in HRT users. This integrated effect supports the hypothesis of a direct hormonal influence on uric acid metabolism, beyond renal clearance alone. Uric acid has been recognized as both a marker and potential mediator of cardiovascular risk, especially in women [2]. In our cohort, the notable SUA difference between HRT users and non-users (1.2 mg/dL) is clinically relevant, considering the known associations of hyperuricemia with hypertension, vascular dysfunction, and mortality [1–3]. The observed benefits in BMI and lifestyle factors further support the positive metabolic profile associated with HRT.

Furthermore, when applying the cutoff value of 5.26 mg/dL, which has been associated with an increased incidence of myocardial infarction in women but not in men, we observed a lower prevalence of hyperuricemia among HRT users compared with nonusers [9]. This finding underlines the lower prevalence of high levels of SUA in women undergoing HRT, further supporting the favorable metabolic profile observed in this group. Importantly, the observation strengthens the hypothesis that HRT may modulate uric acid metabolism, potentially contributing to the reduction of cardiovascular risk in postmenopausal women.

Another critical consideration is the timing and formulation of HRT, which has evolved over recent years. Hodis and Mack emphasize the importance of initiating HRT during the early postmenopausal period to achieve cardiovascular protection [6]. This concept aligns with the “timing hypothesis,” potentially relevant to uric acid metabolism as well [10,11]. Furthermore, these observations raise the hypothesis that current uric acid thresholds used to define hyperuricemia may not adequately reflect sex- and age-specific cardiovascular risk. The impact of hormonal fluctuations, particularly estrogen decline during menopause and subsequent HRT use, suggests the potential need for different uric acid thresholds in women based on menopausal status and hormonal therapy exposure. Establishing such differentiated cut-offs could enhance risk stratification and lead to more tailored prevention strategies in women across the lifespan [12,13].

While this study is cross-sectional and subject to potential confounders, the consistency across endpoints supports biological plausibility. Further investigation is warranted, particularly regarding clinical outcomes and treatment personalization for hyperuricemic postmenopausal women. Finally, our results underline the value of a sex-specific approach to cardiovascular prevention in postmenopausal women, which integrates traditional risk markers with metabolic and hormonal parameters such as SUA.

In conclusions, our findings demonstrate that HRT use is associated

with lower SUA levels and a more favorable cardiometabolic profile in postmenopausal women. These differences remain significant even after normalization for renal function, suggesting a direct hormonal influence on uric acid metabolism. Taken together, these results support a potential protective metabolic role of HRT and point toward the importance of incorporating hormonal status into cardiovascular risk assessment. Future prospective studies are warranted to confirm these associations and to evaluate whether HRT-mediated uric acid reduction translates into improved cardiovascular outcomes.

Author contributions

Conceptualization: AVM, CB; Data curation and formal analysis: CC, VS, GZ; Writing—original draft preparation: AVM, CC, VS, GZ; MN, MP Writing—review and editing: all authors; Supervision: AVM, MN, MP, CB.

What is known about this research topic?

Elevated serum uric acid is a known marker of cardiometabolic risk in postmenopausal women, often rising after menopause due to estrogen decline.

Hormone replacement therapy is hypothesized to lead to lower uric acid levels and improved metabolic profiles.

What this study adds and its future implications

This study shows that HRT users have significantly lower serum uric acid levels and better cardiometabolic profiles than nonusers.

It highlights a strong association between HRT use and reduced cardiovascular risk markers in postmenopausal women.

These findings support reevaluating hyperuricemia thresholds and suggest personalized prevention strategies based on hormonal status.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CB: Given his role as Associate Editor, had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to another journal editor." If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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