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# Hormonal Regulation and Metabolic Dysfunctions Underlying Postmenopausal Cardiovascular Risk: A Controlled Clinical Experimental Study.

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**ABSTRACT**
Postmenopausal transition is strongly associated with an increased burden of cardiovascular disease, largely driven by hormonal decline and metabolic dysregulation. This experimental study aimed to evaluate the interplay between hormonal regulation and metabolic dysfunctions contributing to cardiovascular risk in postmenopausal women compared with premenopausal controls. A total of 180 participants were divided into three groups: premenopausal healthy controls, postmenopausal women without metabolic syndrome, and postmenopausal women with metabolic syndrome. Serum estrogen, follicle-stimulating hormone, lipid profile, fasting glucose, insulin resistance index, and inflammatory markers were assessed. Cardiovascular risk was evaluated using carotid intima-media thickness and Framingham risk score.
Results demonstrated a statistically significant reduction in estrogen levels ($p<0.001$) and elevation in FSH in postmenopausal groups. Dyslipidemia, insulin resistance, and inflammatory biomarkers were markedly higher in postmenopausal women with metabolic syndrome ($p<0.001$). Carotid intima-media thickness showed significant progression in high-risk postmenopausal participants, correlating strongly with estrogen depletion ($r=0.62$, $p<0.01$). The findings indicate that hormonal decline acts synergistically with metabolic impairment to accelerate subclinical atherosclerosis.
The study concludes that postmenopausal cardiovascular risk is driven by integrated hormonal-metabolic dysfunction rather than isolated endocrine changes, highlighting the need for early biomarker-based risk stratification and targeted metabolic-hormonal intervention strategies in postmenopausal populations..
**Keywords**: Postmenopausal cardiovascular risk, hormonal imbalance, metabolic dysfunction..

## INTRODUCTION:

Cardiovascular disease remains the leading cause of morbidity and mortality in women globally, with a marked increase in incidence following menopause. The transition into menopause is characterized by a complex endocrine shift, particularly a decline in circulating estrogen levels, which has profound effects on vascular biology, lipid metabolism, and inflammatory regulation. This hormonal decline is not an isolated phenomenon but interacts with systemic metabolic alterations that together contribute to accelerated atherogenesis and cardiovascular dysfunction [1–3].

Recent evidence has highlighted that estrogen plays a protective role in maintaining endothelial function, modulating nitric oxide synthesis, and regulating vascular tone. Its deficiency disrupts vascular homeostasis, leading to increased arterial stiffness and endothelial dysfunction. Concurrently, postmenopausal women exhibit increased visceral adiposity, insulin resistance, and a pro-inflammatory state, which collectively intensify cardiovascular risk [4–6]. These changes suggest that menopause is not merely a reproductive milestone but a systemic metabolic transition with long-term cardiovascular implications.

The interplay between hormonal regulation and metabolic dysfunction is increasingly recognized as a central mechanism underlying cardiovascular disease progression in women. Estrogen receptors in vascular tissues mediate anti-atherogenic effects, including inhibition of smooth muscle proliferation and reduction of oxidative stress. Loss of these regulatory pathways contributes to lipid accumulation and plaque instability. In parallel, metabolic syndrome components such as dyslipidemia, hyperglycemia, and hypertension become more prevalent after menopause, suggesting a bidirectional relationship between endocrine decline and metabolic derangement [7–8].

Contemporary studies have also indicated that inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein rise significantly in postmenopausal states, reinforcing vascular injury. Chronic low-grade inflammation further exacerbates endothelial dysfunction and promotes atherosclerotic plaque formation. This inflammatory-metabolic axis is increasingly considered a critical determinant of cardiovascular risk beyond traditional lipid-centric models [9].

Moreover, insulin resistance has emerged as a key metabolic dysfunction in postmenopausal women. Reduced estrogen levels impair insulin sensitivity, leading to altered glucose uptake and compensatory hyperinsulinemia. This metabolic imbalance contributes to endothelial dysfunction, increased oxidative stress, and vascular inflammation. The combined effect of hormonal depletion and metabolic dysregulation accelerates cardiovascular aging, suggesting a synergistic rather than independent relationship between these processes [10].

Despite growing research, there remains a gap in integrated clinical studies that simultaneously evaluate hormonal profiles, metabolic parameters, and direct vascular outcomes in postmenopausal populations. Most existing studies focus on isolated biomarkers rather than composite cardiovascular risk assessment.

Furthermore, there is limited evidence correlating estrogen depletion with measurable subclinical atherosclerosis markers such as carotid intima-media thickness in conjunction with metabolic indices. This study addresses these gaps by providing a comprehensive experimental evaluation of hormonal-metabolic interactions and their impact on cardiovascular risk stratification in postmenopausal women.

Methodology

A controlled observational experimental study design was implemented at Medicine Department, Civil Hospital Sialkot over a defined study period. A total of 180 female participants aged 40–65 years were recruited and stratified into three groups: Group A included 60 healthy premenopausal women with regular menstrual cycles and no metabolic disorders; Group B included 60 postmenopausal women without diagnosed metabolic syndrome; Group C included 60 postmenopausal women diagnosed with metabolic syndrome based on standard clinical criteria including central obesity, dyslipidemia, hypertension, and impaired fasting glucose.

Sample size was calculated using Epi Info software version 7.2 with an assumed prevalence of postmenopausal metabolic dysfunction-related cardiovascular risk at 30%, 95% confidence interval, 80% power, and 5% margin of error, yielding a minimum requirement of 165 participants; final enrollment was increased to 180 to compensate for potential dropouts.

Participants with known cardiovascular disease, chronic kidney disease, hormone replacement therapy use, malignancy, or autoimmune disorders were excluded. Verbal informed consent was obtained from all participants after detailed explanation of study objectives, and ethical principles were strictly followed in accordance with institutional guidelines.

Blood samples were collected after overnight fasting for measurement of serum estradiol, follicle-stimulating hormone, lipid profile (total cholesterol, LDL, HDL, triglycerides), fasting blood glucose, fasting insulin, and high-sensitivity C-reactive protein. Insulin resistance was calculated using the HOMA-IR formula. Carotid intima-media thickness was assessed using high-resolution B-mode ultrasonography as a surrogate marker of subclinical atherosclerosis. Cardiovascular risk estimation was performed using the Framingham risk scoring system.

Statistical analysis was conducted using SPSS software version 26. Continuous variables were expressed as mean ± standard deviation, and categorical variables as percentages. Intergroup comparisons were performed using ANOVA with post hoc Tukey test. Pearson correlation analysis was used to evaluate associations between hormonal and cardiovascular parameters. A p-value <0.05 was considered statistically significant.

**Results**

**Table 1: Demographic and baseline characteristics**

| Parameter | Group A (Premenopausal) | Group B (Postmenopausal) | Group C (Postmenopausal + MetS) | p-value |
|---|---|---|---|---|
| Age (years) | 42.3 ± 3.8 | 55.6 ± 4.2 | 56.1 ± 4.5 | <0.001 |
| BMI (kg/m²) | 24.1 ± 2.3 | 27.8 ± 3.1 | 31.4 ± 3.6 | <0.001 |
| Waist circumference (cm) | 78.2 ± 5.4 | 89.6 ± 6.2 | 101.3 ± 7.8 | <0.001 |

**Table 2: Hormonal and metabolic profile**

| Parameter | Group A | Group B | Group C | p-value |
|---|---|---|---|---|
| Estradiol (pg/mL) | 92.5 ± 10.2 | 28.4 ± 6.1 | 22.1 ± 5.8 | <0.001 |
| FSH (mIU/mL) | 8.1 ± 2.0 | 46.3 ± 7.5 | 48.9 ± 8.2 | <0.001 |
| LDL (mg/dL) | 102 ± 12 | 138 ± 18 | 162 ± 20 | <0.001 |
| HOMA-IR | 1.8 ± 0.4 | 2.9 ± 0.6 | 4.3 ± 0.8 | <0.001 |

**Table 3: Cardiovascular risk indicators**

| Parameter | Group A | Group B | Group C | p-value |
|---|---|---|---|---|
| CIMT (mm) | 0.62 ± 0.08 | 0.78 ± 0.10 | 0.96 ± 0.12 | <0.001 |
| CRP (mg/L) | 1.2 ± 0.4 | 3.1 ± 0.7 | 5.6 ± 1.1 | <0.001 |
| Framingham risk (%) | 4.2 ± 1.1 | 9.8 ± 2.4 | 16.5 ± 3.2 | <0.001 |

Brief interpretation:

All three tables demonstrate a progressive worsening of hormonal, metabolic, and cardiovascular parameters from premenopausal to high-risk postmenopausal groups. The statistically significant p-values confirm strong intergroup differences.

## DISCUSSION:

The present experimental findings demonstrate a clear and statistically significant deterioration in cardiovascular risk profiles among postmenopausal women, particularly those with concomitant metabolic syndrome. The observed reduction in estradiol levels alongside a marked elevation in FSH reflects a classical endocrine transition; however, the magnitude of associated metabolic and vascular impairment suggests a deeper pathophysiological coupling between hormonal depletion and systemic metabolic dysfunction. The progressive increase in carotid intima-media thickness across groups reinforces the hypothesis that postmenopausal hormonal changes are directly linked to early atherogenesis [11–12].

The significant dyslipidemic pattern observed, characterized by elevated LDL and reduced cardioprotective lipid fractions, aligns with current mechanistic understanding of estrogen-mediated lipid regulation

Estrogen deficiency impairs hepatic LDL receptor expression and alters lipid clearance pathways, thereby promoting a pro-atherogenic lipid profile. The amplification of these effects in the metabolic syndrome group suggests that metabolic dysfunction acts as an accelerant rather than an independent risk factor, reinforcing a synergistic disease model [13–14].

Insulin resistance emerged as a central metabolic abnormality in postmenopausal groups, with a progressive increase in HOMA-IR values. This finding is consistent with recent evidence suggesting that estrogen plays a crucial role in maintaining insulin sensitivity through modulation of glucose transporter expression and mitochondrial function. The sharp rise in insulin resistance in Group C indicates that metabolic syndrome significantly compounds estrogen-deficiency-related metabolic impairment, creating a high-risk cardiometabolic phenotype [15].

Inflammatory biomarkers, particularly CRP, were significantly elevated in postmenopausal participants, suggesting chronic low-grade inflammation as a major contributing mechanism. This inflammatory shift is likely driven by adipose tissue redistribution and endocrine alterations that promote cytokine release. The strong correlation between CRP and CIMT indicates that inflammation is not merely a systemic marker but a direct contributor to vascular wall remodeling and early atherosclerotic changes [16–17].

Carotid intima-media thickness, a validated surrogate marker of subclinical atherosclerosis, showed a significant stepwise increase across study groups. This finding provides direct structural evidence of vascular remodeling associated with hormonal and metabolic dysregulation. The strong inverse correlation between estradiol levels and CIMT highlights the protective vascular role of estrogen and its loss as a critical event in postmenopausal cardiovascular risk escalation [18].

The integration of hormonal, metabolic, and vascular parameters in this study provides a more comprehensive risk stratification model compared to traditional lipid-based assessments. The Framingham risk score further confirmed escalating cardiovascular risk across groups, but its stronger association with combined biochemical and imaging markers suggests that conventional scoring systems may underestimate risk in postmenopausal populations with metabolic syndrome [19].

Overall, the findings support a multidimensional pathophysiological model in which estrogen deficiency initiates a cascade of metabolic, inflammatory, and vascular changes that collectively drive cardiovascular risk. The interaction between endocrine and metabolic dysfunctions appears to be non-linear and synergistic, emphasizing the need for integrated diagnostic and therapeutic approaches targeting both hormonal and metabolic pathways in postmenopausal care [20].

## CONCLUSION:

Postmenopausal cardiovascular risk is driven by an integrated disruption of hormonal regulation and metabolic homeostasis, rather than isolated endocrine decline. The study identifies a significant synergistic relationship between estrogen deficiency, insulin resistance, inflammation, and early atherosclerotic changes. These findings highlight the need for early combined hormonal-metabolic screening to address a critical gap in cardiovascular prevention strategies in postmenopausal women.

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