Effect of Sex Hormones on Cholesterol Crystallization: Implications for Gender Differences in Cardiovascular Events

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Abstract

Background: The cardiovascular system is influenced by sex hormones, with women experiencing a protective effect against cardiovascular events before menopause. Cholesterol serves as the primary structural component of many sex hormones, while cholesterol crystals play a role in triggering cardiovascular events by expanding within plaque cores during crystallization, thereby disrupting the fibrous cap and causing heart attacks and strokes.

Objectives: The aim of this study is to investigate the impact of estrogen, progesterone, and testosterone on the formation and growth of cholesterol crystals (CCs) during crystallization, which plays a crucial role in the development of atherosclerosis and plaque rupture leading to heart attacks.

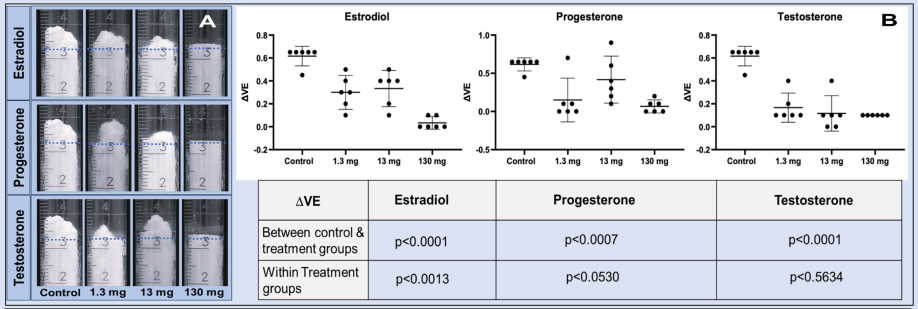
Methods: Various concentrations of estrogen, progesterone, and testosterone were utilized to assess their effects on the formation and peak volume expansion (ΔVE) of cholesterol crystals after melting with heat gun and then crystalizing at room temperature. Hormone doses ranged from 13 µg to 130 mg, and ΔVE was compared to samples without hormone supplementation. Samples of crystals from different treatment groups, as well as fresh atherosclerotic human plaques incubated with and without hormone, were examined using scanning electron microscopy (SEM) to evaluate their impact on crystal morphology.

Results: Addition of sex hormones to cholesterol resulted in a significant inhibition of ΔVE in a dose-dependent manner **(Fig 1)**. Particularly, estrogen exhibited the most potent effect even at lower doses compared to testosterone and progesterone (p=0.001 vs p=0.053, p=0.563) respectively. **(Fig 1)** SEM analysis revealed that CCs from hormone-treated samples, both in test tubes and human plaques, exhibited signs of dissolution with a loss of sharp edges compared to untreated specimens, except for testosterone which did not demonstrate dissolving crystals in treated carotid plaque samples **(Fig 2)**.

Conclusions: Given the critical role of CCs in triggering plaque rupture, the inhibition of their formation, expansion, and alteration of their morphology may represent an additional mechanism underlying the effectiveness of sex hormones in reducing cardiovascular risk, especially in premenopausal women.

Disclosure: Human studies were conducted under Michigan State University IRB # 0518 approval, adhering to local legislation and institutional requirements.

Results



ΔVE	Estradiol	Progesterone	Testosterone
Between control & treatment groups	p<0.0001	p<0.0007	p<0.0001
Within Treatment groups	p<0.0013	p<0.0530	p<0.5634

Figure 1. A) Decrease in volume expansion with increasing dose of sex hormones compared to control. **B)** Different concentration of estradiol (p=0.0013) and progesterone (p=0.0530) showed significant decreases in ΔVE. Conversely, the addition of different concentrations of testosterone (p=0.5634) did not result in a substantial alteration in ΔVE, as analyzed by ANOVA. ΔVE denotes the decrease in volume expansion (B).

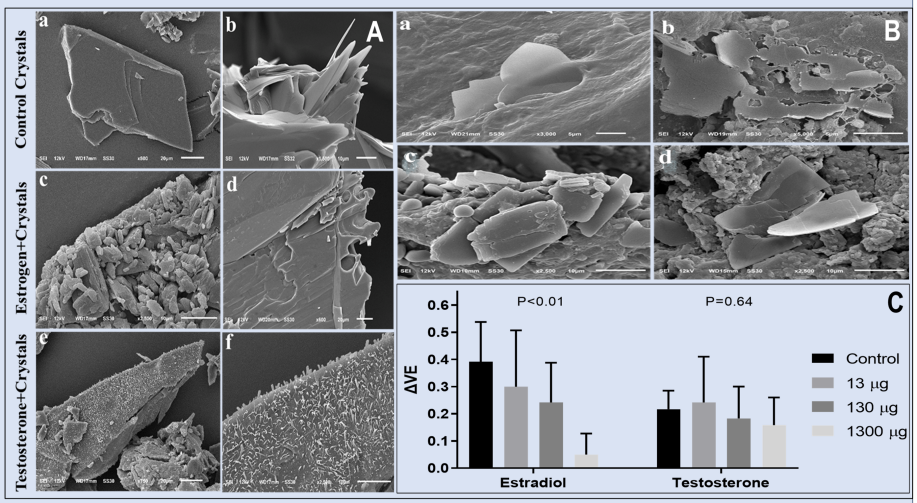


Figure 2: A) SEM of cholesterol crystals without hormones (a,b) and after incubation with estrogen (c,d) and testosterone (e,f). Estrogen and testosterone both dissolve crystals. **B)** SEM of human atherosclerotic plaques exposed to estrogen and testosterone. Crystals in estrogen exposed arterial plaques displayed loss of sharp edges and had disrupted surfaces (b) compared to the untreated samples (a). Testosterone treated carotid plaques did not show dissolving crystals or change in morphology (c,d). **C)** Graphic demonstrating significant reduction in volume expansion (ΔVE) with low dose estradiol but not with low dose of testosterone.

Conclusions

- This study suggests a potential mechanism by which estrogens could provide cardio-protection in pre-menopausal women, independent of LDL-c reduction.
- ΔVE during cholesterol crystallization can promote atherogenesis and cardiovascular events by causing volume expansion and sharp morphology within plaques.
- Higher levels of estrogen and progesterone may mitigate the injurious effect of CCs and may help explain the protective impact of pre-menopausal estrogen levels on cardiovascular events.
- Future treatments for cardiovascular disease may hold promise for cholesterol crystal-dissolving hormone therapy and other interventions aimed at limiting cholesterol crystallization.

References

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