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Follicle-stimulating hormone is responsible for androgen deprivation therapy associated atherosclerosis by exaggerating endothelial inflammation

Eur Urol Suppl 2019; 18(1);e72

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Introduction & Objectives: Androgen deprivation therapy (ADT) has been the standard treatment for locally advanced or metastatic prostate cancer (PCa). Orchiectomy, gonadotropin-releasing hormone (GnRH) agonist, and antagonist are three major types of ADT. Unfortunately, recent studies suggest that ADT correlates with an increased risk of cardiovascular diseases (CVDs), which prove to be most common cause of mortality in men with early-stage PCa. Atherosclerosis is one of the predominant causes of CVDs. Previous researches show that testosterone deficiency is associated with adverse cardiovascular risk profiles and mortality, however, it could not explain why GnRH antagonist lowered risks of CVDs compared to GnRH agonist. As such, there is a critical need to identify other mechanisms that drive the development of CVDs in addition to testosterone. Cause transient or long-term follicle-stimulating hormone (FSH) elevation is common during ADT. We aim to explore the role of FSH in ADT-induced atherosclerosis and identify its potential mechanisms, thus developing novel preclinical approaches to enhance the effects of endocrine therapy.

Materials & Methods: Male ApoE$^{-/-}$ mice fed with western diet were treated with gonadotropin-releasing hormone (GnRH) agonist, leuprolide, or antagonist, degarelix to observe ADT-induced atherosclerosis. Human umbilical vein endothelial cells (HUVECs) were treated with FSH and tumor necrosis factor alpha (TNFa) to examine FSH function in endothelial inflammation and underlying mechanisms. Surgically castrated ApoE$^{-/-}$ mice were treated with testosterone and FSH to examine role of FSH in atherosclerosis development. ApoE$^{-/-}$ mice treated with leuprolide were given anti-FSHβ antibody to verify FSH "flare up" in atherosclerosis progression.

Results: We demonstrated that GnRH agonist, surgical castration or FSH supplementation induced more serious atherosclerotic lesions. Inhibition of FSH activity with anti-FSHβ antibody greatly alleviated atherosclerosis progression. In vitro data showed that FSH, synergizing with TNF-α, amplified inflammatory response by promoting vascular cell adhesion protein 1 (VCAM-1) expression via cAMP/PKA/CREB and PI3K/AKT/GSK-3β pathways induced c-Jun and GATA-6 activation.

Conclusions: ADT-induced FSH elevation, either transient or long-term, accelerates atherosclerosis progression by exaggerating endothelial inflammation. New therapies targeting FSH should be developed to help clinicians avoid CVD risks in ADT patients.