Cardiometabolic Effects Associated With Androgen Deprivation Therapy: Potential Mechanisms of Action

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BACKGROUND

- Androgen deprivation therapy (ADT) may be associated with increased cardiovascular (CV) morbidity and mortality in patients with advanced prostate cancer[1-4]
- Although gonadotropin-releasing hormone (GnRH) receptor agonists and antagonists both reduce testosterone to castrate levels, recent studies suggest that there may be differences in CV risk between GnRH receptor agonists and antagonists[5,6]
  - A meta-analysis of six phase 3 studies reported a significantly lower risk of cardiac events in men with preexisting CV disease within 1 year of initiating treatment with a GnRH receptor antagonist compared with treatment with a GnRH receptor agonist (hazard ratio = 0.44; $P = 0.002$)[5]
  - A separate meta-analysis of results from five phase 3 studies found that treatment with the GnRH receptor antagonist degarelix was associated with a lower incidence of severe CV side effects compared with treatment with GnRH receptor agonists (1.6% vs 3.6%; odds ratio = 0.55; P = not significant)[6]
- Differences in the mechanism of action between GnRH antagonists and agonists may be responsible for the different cardiometabolic profiles associated with forms of ADT
- Data from a clinical trial demonstrated that degarelix more effectively suppressed serum levels of follicle-stimulating hormone (FSH) compared with the GnRH receptor agonist leuprolide[7]
- FSH is thought to promote the development of inflammation, adiposity, insulin resistance, and atherosclerosis[8]; therefore, we sought to develop a model that would help us better understand how FSH contributes to the cardiometabolic morbidity observed with ADT

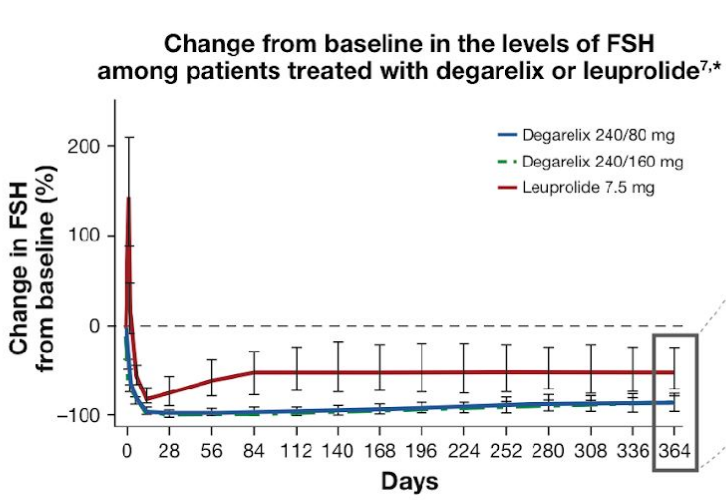
OBJECTIVE

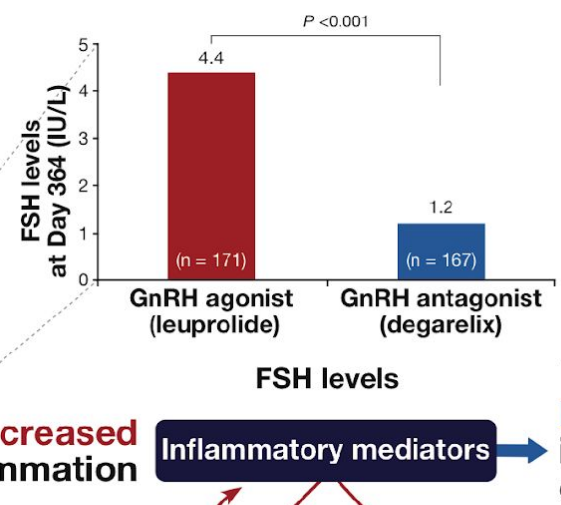
- To develop a model explaining the mechanisms mediated by FSH that contribute to the cardiometabolic effects observed during ADT with GnRH receptor agonists and antagonists

CONCLUSIONS

- **Emerging evidence suggests that proinflammatory markers can be potentially driven by FSH and may contribute to differing cardiometabolic effects in ADT**
- **FSH levels were more suppressed with a GnRH receptor antagonist versus agonist[7]**
- **The model hypothesizes the importance of FSH as a biomarker when treating patients at risk for adverse cardiometabolic events with ADT**
- **Further insights into the mechanisms underlying the cardiometabolic events resulting from ADT are being investigated**

GnRH antagonists decrease FSH more than GnRH agonists: potential differences in cardiometabolic effects associated with ADT.



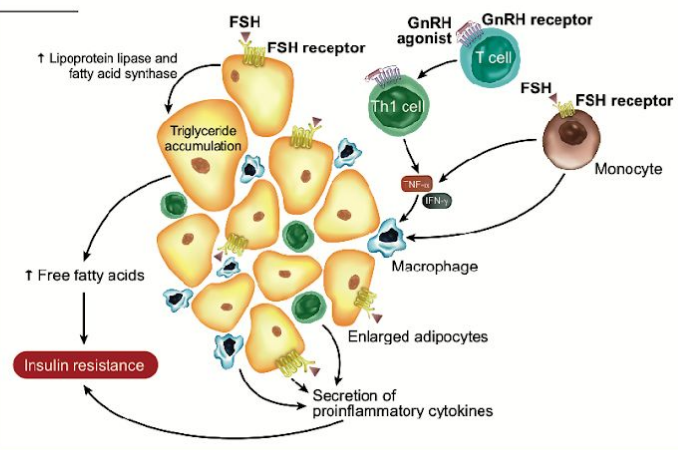


- Inadequate FSH control during ADT may contribute to profound metabolic differences between GnRH receptor agonists and antagonists, resulting in cardiometabolic morbidity
- FSH has been shown to stimulate secretion of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6)[9,10]
- T-cell activation by GnRH receptor agonists induces a shift toward the type 1 T helper (Th1) phenotype associated with proinflammatory states[11,12]

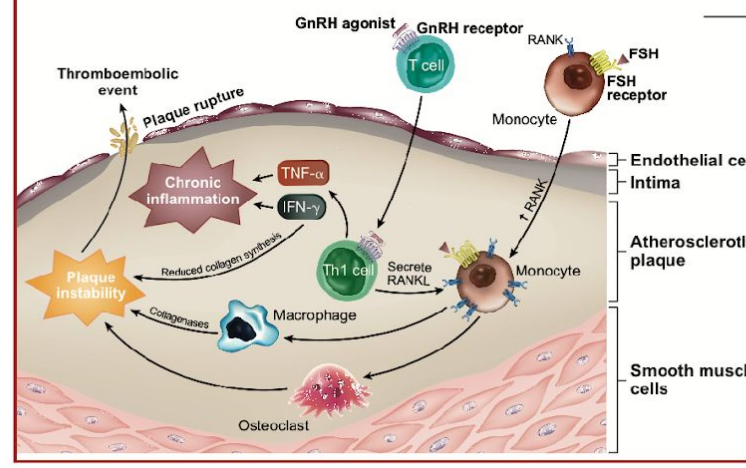
Increased inflammation → **Inflammatory mediators** → **Less inflammation and risk of CV events compared with GnRH agonist**

- FSH stimulation promotes lipid accumulation in adipose tissue in a concentration-dependent manner[13]
  - Altered adipose tissue further contributes to inflammation through the overexpression of TNF-α and IL-6[14-16]
  - FSH levels have been shown to positively correlate with body mass index[13]
- Increased secretion of free fatty acids and pro-inflammatory cytokines leads to insulin resistance; this altered insulin action contributes to hypertriglyceridemia and non-alcoholic fatty liver disease[17-20]

FSH and GnRH in Adipose Tissue Accumulation



FSH and GnRH in Atherosclerosis/Plaque Instability



- Heightened release of proinflammatory cytokines is linked to increased CV risk through promotion of atherosclerosis and plaque instability[14,21]

METHODS

- A colloquium of experts in the treatment of prostate cancer was convened in May 2015 to discuss the current knowledge of FSH and its potential relationship with the undesirable cardiometabolic effects associated with ADT
- An in-depth review of preclinical and clinical literature in Medline and PubMed was conducted on specific topics of interest; this poster describes findings relevant to the mechanisms by which FSH may mediate the cardiometabolic effects of ADT

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*Figure reproduced from Klotz L, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. *BJU Int.* 2008;102(11):1531-1538, with permission from John Wiley and Sons.

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