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CLINICAL STUDY

Androgen deprivation therapy and cardiovascular complications

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ABSTRACT
Cardiovascular complications associated with the use of antiandrogens have already been known for some time. Based on the results of the latest meta-analyses and clinical studies published in the last few years, the attention of the scientific community is focused on the deleterious cardiovascular effects of gonadotropine-releasing hormon agonists in context of the androgen deprivating therapy. The cardiac toxicity is a problem especially in patients with preexisting cardiovascular comorbidities. Increased arterial wall thickening along with endothelial dysfunction has been observed in patients with descreased androgens levels in the peripheral blood. The treatment with gonadotropine-releasing hormon agonists may disrupt the intracellular concentration of calcium ions and the contractile process and potentially result in pathological remodelling of heart. Here, we give several possible mechanisms of action of gonadotropine-releasing hormon agonists on the cardiovascular system that may be a potential explanation of the clinical observations *(Ref. 44).* Text in PDF *www.elis.sk.*
KEY WORDS: androgen deprivation therapy, cardiovascular risk, gonadotropine-releasing hormon agonists, prostate cancer, testosterone.

Introduction

Prostate cancer is the most common cancer in men. The core management of localized prostate carcinoma is presented by radical prostatectomy or radiotherapy optionally combined with androgen deprivation therapy (ADT) in neoadjuvant and adjuvant regimens (1). A blockade of testosteron production by bilateral orchiectomy or treatments with gonadotropine-releasing hormon (GnRH) agonists and antagonists are the base of ADT.

ADT decreases testicular synthesis of androgens as well as their circulating levels. This reduces the availaibility of androgen receptor ligands resulting in the diminished proliferation in prostate cancer. Unfortunately, ADT has also an adverse effects on cardiovscular system.

According to several authors an increased attention should be given to patients with a history of cardiovascular problems (2–5). The study by Keating et al (6) is one of the landmark studies investigating ADT associated cardiovascular risk. The observation study included 73,196 men with prostate carcinoma. The men treated with GnRH agonists showed an increase of 16 % in coronary heart disease, an increase of 11 % in myocardial infarction and an increase of 16 % in sudden cardiac death in comparation with those with no hormonal treatment (6). Daskavich et al (7) published long-term follow-up of the Prostate Cancer Outcomes Study showing that older men (aged ≥ 60 years) with multiple comorbidities are far more likely to die from other causes than prostate cancer. On the other hand, some studies have found no association between ADT and increased cardiovascular risk or morbidity (8–14). Thus, the relationship between ADT and cardiovascular diseases remains still controversial. An increased risk of myocardial infarction in large cohort studies has been shown (15–17). Outcomes of studies related to heart failure are less consistent. Results of the two registers showed an association between ADT and heart failure, but it was not confirmed by another register (5). Following many observations, a science advisory consensus statement on GnRH agonist therapy and cardiovascular risk was issued, and the US Food and Drug Administration safety warns addresing the concern of increased risk of myocardial infarction, stroke and sudden cardiac death (18).

ADT induces a dysmetabolic state by increasing LDL cholesterol levels, triglycerides, inflammation and insulin resistance, however, these changes do not explain the observed significant increase in cardiovascular risk during ADT. Currently, the extent of the association of ADT negative effect on the cardiovascular system with decreased testosterone levels is not clear. Testosterone has numerous positive and also negative effects on the heart and vessels. Positive testosterone effects on heart include cardioprotection (cytoprotection), vasodilation, antiarrhytmic effect, maintainance of lipid and glucose levels and inhibition of atherosclerosis (19). But GnRH agonist therapy is not effective in permanent long-term decrease of body testosterone. It was proven that even in castrated individuals the intracellular levels of androgens increase. It could

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be due to increased levels of intraprostatic cholesterol („in situ conversion“) (20, 21).

In this way we still do not know exactly if the testosterone is “the only culprit”. The difference in testosterone concentration is important not only for the purpose of monitoring a tumor but also as a possible molecule for monitoring of long-term adverse effects related to GnRH agonists.

The aim of this review paper is to discuss currently known effects of GnRH agonists administration on cardiovascular system.

Effects of GnRH and its analogs on hormonal production and receptors

The effects of GnRH agonists were analyzed in diverse studies carried out since 1976. GnRH is secreted in pulse manner by the hypothalamus. It stimulates the pituitary releasing of luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH subsequently stimulates testosterone secretion, predominantly by the testes. GnRH agonists bind to GnRH receptors and initially result in marked increases of FSH, LH, testosterone and DHT, but after 1 to 3 weeks of treatment suppres testosterone to < 0.5 ng/ml (< 1.7 nmol/l). A part of the group of patients (5–17 %) receiving GnRH agonists fail to achieve the castrate level of testosterone. Sustained pituitary overstimulation by GnRH agonists causes a downregulation of GnRH receptors and an uncoupling of the GnRH signal transduction mechanism (22). A decrease in LH and FSH, together with the downregulation of gonadal receptors for LH and FSH, causes a complete inhibition of testicular function. But it has been detected that FSH rises gradually during GnRH agonist treatment (23). Also the loss of GnRH receptor sensitivity during long-term agonist therapy can cause restored testosterone production (24).

GnRH agonists are degraded and eliminated from plasma more slowly than natural GnRH. Studies with labeled GnRH analogs detected accumulation of these substances primarily in the liver and kidneys (the main degrading organs), and in the pituitary (the biologic target) (22). GnRH receptor is relatively highly expressed in the pituitary, breast, prostate, kidney, thymus, in lymphocytes and at lower levels in a variety of other organs. Detection of GnRH receptor in these tissues suggests that GnRH agonists may also have direct actions on peripheral targets but their role in extrapituitary tissues is unknown (25).

GnRH agonists and a potential risk of cardiovascular dysfunction

To date, relationship between GnRH agonists and cardiovascular diseases is still not well understood. One theory states that this therapy exacerbates preexisting cardiovascular (CV) risk factors and makes them more evident during the treatment. Main side effects caused by chronic administration of GnRH agonists are those that can be attributed to reduced levels of circulating testosterone. Lower testosterone levels associated with ADT can result in the accumulation of fat and a decrease in muscle. Adipokines produced in adipose tissue contribute to insulin resistance and to development of metabolic syndrome. Patients with metabolic syndrome have two-fold increased cardiovascular disease risk and it worths a mention that men with metabolic syndrome often have low testosterone levels (26). Several trials have shown that elevating of low testosterone levels may improve the conditions of metabolic syndrome and modify CV risk factors. Abnormal lipid profiles, elevation of pro-inflammatory factors, hypertension, insuline resistance and endothelial dysfunction are common features in men with testosterone deficiency.

Prolonged absence of male sex hormones causes the structural and functional cardiac remodeling. Gonadectomy leads to concentric heart remodeling characterized by increased left ventricular posterior wall, reduced left ventricular internal diameter in diastole, and increased relative wall thickness (27). The absence of androgens after myocardial infarction can lead to increased apoptosis of cardiomyocytes, more extensive remodeling and impaired left ventricular function (28). Long-therm testosterone deprivation attenuates the process of repolarization. Gonadectomy may reduce calcium ions influx in heart, sarcoplasmic reticulum Ca^{2+} content in myocytes, but levels of sarcoplasmic reticulum Ca^{2+}-binding proteins calsequestrin and calreticulin are not affected by gonadectomy. Expression of cardiac protein SERCA2a is not affected by gonadectomy as well. Androgens modulate cAMP/PKA and CaMKII pathways. Gonadectomy leads to reduction of phosphorylation of phospholamban at the CaMKII site and the proteinkinase A-site (27). Testosterone deprivation has no effect on myofilament Ca^{2+} sensitivity but decreases the maximal myofilament responses to Ca^{2+}. Gonadectomy causes a shift from the fast α-myosin heavy chain isoform to the slower ß-myosin heavy chain isoform and this effect can be reversed by testosterone replacement (29). Mice treated with GnRH agonists had more visceral fat and larger atherosclerotic plaques than mice with GnRH antagonist treatment. In preclinical animal models GnRH agonists cause an increased risk of plaque instability (30). The risk of plaque rupture is increased by IFN-γ. Activation of GnRH receptors on T-lymphocytes stimulates T cell proliferation and differentiation towards Th1 phenotype producting IFN-γ. Therefore, it can be hypothesized that the stimulation of GnRH receptors by GnRH agonists may increase destabilization of atherosclerotic plaques, rupture risk and subsequent thrombotic complications including myocardial infarction and ischemic stroke. The destabilization of established atherosclerotic lesions may explain the short-term adverse effect of GnRH agonist therapy on cardiovascular complications risk, potentially driven by stimulation of GnRH receptors on T lymphocytes (17).

For summary, GnRH agonists can cause a damage to heart and vessels by two mechanisms. The direct way is related to the presence of GnRH receptors in the myocardium. Indirectly it acts through increased body weight, insulin resistance and lipidemia changes.

Receptors for all major sex steroid hormones are present on individual cardiomyocytes so these hormones may influence heart at the cellular level. GnRH controls the contraction of cardiomyocytes itself by a mechanism that is dependent on the GnRH receptor / proteinkinase A signaling pathways. The proteinkinase A-mediated pathway promotes cardiomyocyte contractile function, including the L-type Ca^{2+} channel on the sarcolemma and contrac-

tile apparatus components. This proteinkinase also phosphorylates ryanodine receptors and Ca^{2+}-releasing channels in cardiomyocytes. Higher doses of GnRH elevated resting intracellular Ca^{2+} level, increased sarcoplasmic reticulum Ca^{2+} release and cardiac contractility (31). So GnRH agonists treatment may disrupt the intracellular calcium ions level and contractile process can have important role in pathological cardiac remodeling (16). Chronic GnRH agonist therapy may prolong QT interval (6).

GnRH agonists have differential effects on LH and FSH levels. In men, FSH receptor is expressed in testicular Sertoli cells, at low levels in the endothelial cells of the testis as well as in cardiac myocytes. During GnRH agonist treatment FSH is increased gradually (23). At present, we cannot describe an association between FSH levels and CV disease (32).

Clinical studies

Outcomes from studies about still-unresolved question of association of GnRH agonist therapy with increased risk of CV diseases can be problematic due to missing data (type of ADT, cardiovascular disease severity, risk factors). Recent study by O'Farrell and collegues et al (33) analyzed CV disease risk among 41 362 men with ADT because of prostate cancer and 187 785 men without prostate cancer. This study was unique because researchers had access to a drug register and defined ADT type and duration and the patients´ history of cardiovascular disease. Further studies with more detailed and accurate data are needed to better address this issue.

A meta-analysis of observational studies of relationship between ADT and CV diseases revealed that GnRH agonists were associated with a 38 % increased risk of any type of nonfatal CV disease compared with men having prostate carcinoma without therapy. Associations between GnRH agonists and nonfatal or fatal myocardial infarction (MI) or stroke were even 57 % and 51 % (17). Martin-Merino et al (34) found that a combined treatment, GnRH agonists and antiandrogens in patients with prostate cancer increases risk of acute myocardial infarction (OR 3.57; 95% CI 1.44, 8.86). A study by Gandaglia et al. (35) in patients with non-metastatic prostate carcinoma (n = 140 474) reported acute MI (hazard ratio (HR): 1.10; $p < 0.001$) and sudden cardiac death (HR: 1.18; $p < 0.001$). This increased risk in the range of 1.11 and 1.19 was similar to the levels of risk found by Keating et al (6).

ADT was associated with early onset of fatal MI in men aged ≥ 65 years or men with treatment more than 6 months compared with men who were not treated with ADT (36). The increased risk of CV death is not limited to older men (> 65 years), but a similar risk was found in younger men (37). The increased risk of developing CV diseases in men with prostate cancer and treated with GnRH agonists was shown also by a recent study (33). Authors also found that the risk for developing a CV disease was the highest during the first 6 months of the treatment in men who experienced two or more cardiovascular events before they started the therapy with agonists of GnRH. This supports the opinion that those patients threated with ADT and an preexisting CV disease may be at the greatest risk (2–5, 33). Increased cardiovascular toxicity in patients undergoing a short-term ADT was confirmed by another authors (38). During long-term agonist therapy the loss of GnRH receptor sensitivity may occur what can be accompanied with renewal of testosterone production (24) and this fact may partially clarify these results. Older studies also found CV problems mostly within the first 12 months after ADT initiation (36, 39).

Swedish population study (n = 62 500) confirmed that prostate cancer patients compared to patients without prostate cancer had a higher risk of death from heart failure. Moreover, the heart failure was just one cause of death from all CV causes (40). In particular, the HR for heart failure in patients with prostate cancer was higher in the patients being more then 5 years after cancer diagnosis (HR 1.27; 95% CI, 1.18–1.36) compared to those being less then 5 years after diagnosis (HR 1.07; 95% confidence interval CI, 0.99–1.16).

Antiandrogen monotherapy was associated with decreased mortality from congestive heart failure in comparison with the GnRH agonist monotherapy and the combination of GnRH agonist and antinadrogen (41). The therapy combination including GnRH agonist and antiandrogen has been associated with increased prevalence of heart failure (OR 3.19, 95% CI 1.10, 9.27) and hospitalization for heart failure (OR 3:39; 95% CI 1.7, 10.70) compared to patients without this combined treatment (34). In two randomized studies ADT was associated with increased number of episodes of heart failure compared to placebo (42, 43).

Meta-analysis of Carneiro et al (15) evaluated ADT effect on CV complications from 13 trials (n = 137 658). Authors concluded that ADT in patients with prostate cancer (therapy for at least 6 months) increased CV morbidity for acute MI as well as increased incidence of non-fatal events such as arrhythmias, stroke, non fatal myocardial infarction, heart failure, and thrombosis. In the view of these results, the authors believe that ADT is associated with significant adverse effects, and patients on ADT should be regularly monitored by a cardiologist (15). The latest recommendations for the management of patients for ADT-related cardiotoxicity was published by Edelman et al (5) in the journal The Clinical Genitourinary Cancer. In patients with high-risk prostate cancer and a history of heart failure can be shortening of GnRH therapy suitable. But the association between duration of treatment and the incidence of fatal CV events was not confirmed (12). Currently available evidence indicates that ADT in patients with prostate cancer may reveal the patients with risk of subclinical heart failure or worse existing heart failure.

The main way the ADT may increase the risk of a CV disease is by decreasing the levels of circulating testosterone. Testosterone is generally a vasodilator, however, under certain condition it may function as a vasoconstrictor (19). As an arterial vasodilator, testosterone improves myocardial ischemia in men with ischemic heart disease (44). Testosterone deficiency is a common finding in patients with ischemic disease (15). From a systemic view, testosterone has both, beneficial and negative impact on CV system.

Conclusion

The use of GnRH agonists in the treatment of prostate cancer is associated with an increased risk of cardiovascular complica-

tions. Further studies with more detailed and accurate data are needed to predict cardiovascular morbidity and mortality and, in this way, to better define the groups of patients who may benefit from ADT in the form of GnRH agonists. Recent studies suggest that GnRH antagonists could be a good alternative to GnRH agonists for men with a pre-existing CV disease. Moreover, human and basic biological studies are still needed to determine the mechanism responsible for risk associated with the use of GnRH agonists on cardiovascular system.

The urgency to address serious problems pushes often the less significant issues into the background for later investigation. The principle of sophisticated treatment is an elimination of the „unwanted" while protecting what is working well and benefits the body.

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