Published in final edited form as:
BJU Int. 2008 June ; 101(11): 1335–1336. doi:10.1111/j.1464-410X.2008.07707.x.

GONADOTROPHIN-RELEASING HORMONE AGONISTS, DIABETES AND CARDIOVASCULAR DISEASE IN MEN WITH PROSTATE CANCER: WHICH METABOLIC SYNDROME?

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INTRODUCTION

In 2006, we first reported that GnRH agonists were associated with a greater risk of diabetes and cardiovascular disease (CVD) in men with prostate cancer [1]. We studied the records of 73 196 men in the linked Surveillance, Epidemiology and End Results (SEER) and Medicare database who were diagnosed with local or local-regional prostate cancer during 1992–1999. Using a time-varying Cox proportional hazards model that adjusted for patient and tumour characteristics, the current use of a GnRH agonist was associated with a significantly greater risk of incident diabetes, coronary heart disease, myocardial infarction and sudden death. The adjusted hazard ratios for incident diabetes and coronary heart disease were 1.44 and 1.16, respectively. A subsequent study using SEER-Medicare data also reported a significant association between GnRH agonists and incident CVD [2].

Several mechanisms could contribute to greater risk of diabetes and CVD during GnRH-agonist therapy. GnRH agonists increase fat mass and decrease lean body mass [3–5]. Notably, subcutaneous fat accounts for most of the treatment-related fat accumulation [4,6]. GnRH agonists increase serum low- and high-density lipoprotein cholesterol, and triglycerides [4,7,8]. GnRH agonists increase fasting plasma insulin levels [8,9] and decrease insulin sensitivity [10], a marker of insulin resistance.

Insulin resistance is a common metabolic abnormality that underlies type 2 diabetes mellitus and is prevalent in about a quarter of non-diabetic men [11]. Importantly, insulin resistance is an independent risk factor for CVD [12,13]. The metabolic syndrome refers to a clustering of specific CVD risk factors the pathophysiology of which appears to be related to insulin resistance. The National Cholesterol Education Program's Adult Treatment Panel (NCEP ATP III) and WHO define the metabolic syndrome using different but related criteria [14], summarized in the Appendix.

A recent cross-sectional study reported a higher prevalence of the metabolic syndrome (as defined by NCEP ATP III) in 18 men receiving a GnRH agonist than in age-matched control groups of untreated men with prostate cancer, and men without prostate cancer [15]. Men

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CONFLICT OF INTEREST
None declared.

receiving GnRH agonist therapy were more likely to have increased abdominal girth, elevated triglycerides, and elevated fasting plasma glucose, consistent with results of prospective studies of GnRH agonist treatment. However, by contrast with the metabolic syndrome, prospective studies showed that GnRH agonists preferentially increase subcutaneous rather visceral abdominal fat, and increase rather than decrease high-density lipoprotein cholesterol [4]. In addition, the metabolic syndrome is characterized by low levels of adiponectin and elevated markers of inflammation, whereas GnRH agonists significantly increase serum adiponectin levels and do not alter levels of C-reactive protein or other markers of inflammation [6,16]. These observations from prospective trials suggest that GnRH agonists cause a pattern of metabolic changes that is distinct from the classically defined metabolic syndrome.

What are the practical implications of distinguishing the phenotype of men receiving GnRH agonist treatment from the classic metabolic syndrome? The clinical use of the composite definition(s) of the metabolic syndrome centres on its potential value as a risk factor for CVD. However, the metabolic syndrome is imprecisely defined and might have limited independent value as a marker of CVD risk [17,18]. Given these limitations and the distinct metabolic changes associated with GnRH agonist treatment, we recommend evaluation and treatment of individual risk factors for diabetes and CVD with no regard for whether an individual meets the criteria for the diagnosis of metabolic syndrome. Also, these observations suggest that future research should focus on better characterizing the impact of treatment-related metabolic changes on clinical outcomes, and developing effective strategies to prevent treatment-related diabetes and CVD in prostate cancer survivors.

Abbreviations

CVD	cardiovascular disease
SEER	Surveillance, Epidemiology and End Results
NCEP ATP III	National Cholesterol Education Program Adult Treatment Panel III

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APPENDIX

Definitions of the metabolic syndrome for men.

NCEP ATP III

Any three or more of the following:

1. Waist circumference >102 cm
2. Serum triglycerides ≥1.7 mmol/L
3. Blood pressure ≥130/80 mmHg
4. High-density lipoprotein cholesterol <1.0 mmol/L
5. Serum glucose ≥6.1 mmol/L (≥5.6 mmol/L might be applicable)

WHO

Diabetes, impaired fasting glucose, impaired glucose tolerance, or insulin resistance and at least two of the following criteria:

1. Waist to hip ratio >0.90
2. Serum triglycerides ≥1.7 mmol/L
3. Blood pressure ≥140/90 mmHg

4. Urinary albumin excretion rate >20 μg/min or albumin-to-creatinine ratio ≥30 mg/g