

ADT and the metabolic syndrome: no good deed goes unpunished

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Although androgen deprivation therapy (ADT) has been used for more than half a century to treat prostate cancer, its mechanism and associated side effects are continuously updated. Androgens are key players in glucose homeostasis and lipid metabolism. In fact, lower total testosterone predicts a higher incidence of the metabolic syndrome, a cluster of risk factors predisposing patients to late onset diabetes mellitus, atherosclerosis and cardiovascular (CVS) morbidity and mortality.¹ Since CVS disease is the most common competing cause for mortality, we should make all efforts to minimize our iatrogenic contribution to the metabolic syndrome and familiarize ourselves with the growing body of evidence linking ADT to the metabolic syndrome.^{2,3} Mohamedali and colleagues present their experience with the impact of long-term ADT on blood glucose levels in non-diabetic prostate cancer patients. The authors demonstrated that 1 year of ADT use is associated with elevated fasting glucose levels.⁴ This data is in line with a recent review of the ADT/metabolic syndrome which showed a clear casual association between ADT and diabetes mellitus, but the causal association is not as strong with CVS morbidity.⁵ The link needs to be better explored as novel ADT strategies are about to change our practice. In recent years it has become clear that current modes of castration are far from optimal in achieving complete androgen deprivation in prostate cancer cells. Multiple pre-clinical evidences suggest that prostate cancer cells can produce androgens which activate the androgen receptor already in concentrations lower than those traditionally defined as castrated serum testosterone levels (<20 ng/dL). Accordingly, although not completely validated, clinical observations suggest the lower the testosterone level under ADT, the longer the survival;⁶ it is possible that even lower levels of testosterone within and it is possible that even transient events of testosterone break through within the framework of ADT can accelerate disease progression.⁷ Hence, the current trend in ADT is a more strict deprivation of androgens in castrate resistant prostate cancer, and what we used to define as maximal androgen blocked (MAB) will certainly be expanded with the introduction of novel products, such as arbiraterone and MDV3100. It is reasonable

to expect that novel therapeutic strategies that induce more effective testosterone suppression will reciprocally accentuate the metabolic side effect profile of ADT. Data comparing the long-term metabolic side effect of different modes of castration is currently limited,⁸ but once available, should better guide us in treating patients with known risk factors for CVS disease. We should incorporate routine baseline and follow-up assessments of metabolic measurements (fasting glucose levels, lipids, BMI) and advocate lifestyle modification for our ADT patients. We should also stay tuned for potentially more detrimental metabolic side effects with more strict MAB regimens.

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References

1. Saad F, Gooren L. The role of testosterone in the metabolic syndrome: a review. *J Steroid Biochem Mol Biol* 2009;114:40-3.
2. Braga-Basaria M, Dobs AS, Muller DC, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *J Clin Oncol* 2006;24:3979-83.
3. Pinthus JH, Trachtenberg J, Klotz LH. Cardiovascular effects of androgen depletion and replacement therapy. *Urology* 2006;67:1126-32.
4. Mohamedali HZ, Breunis H, Timilshina N, et al. Changes in blood glucose and cholesterol levels due to androgen deprivation therapy in men with non-metastatic prostate cancer. *Can Urol Assoc J* 2011;5:28-32; DOI:10.5489/auaj.09172
5. Faris JE, Smith MR. Metabolic sequelae associated with androgen deprivation therapy for prostate cancer. *Curr Opin Endocrinol Diabetes Obes* 2010;17:240-6.
6. Gomella LG. Effective testosterone suppression for prostate cancer: is there a best castration therapy? *Rev Urol* 2009;11:52-60.
7. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. *J Urol* 2007;178(4 Pt 1):1290-5.
8. Smith MR, Klotz L, Persson BE, et al. Cardiovascular safety of degarelix: results from a 12-month, comparative, randomized, open label, parallel group phase III trial in patients with prostate cancer. *J Urol* 2010;184:2313-9.

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