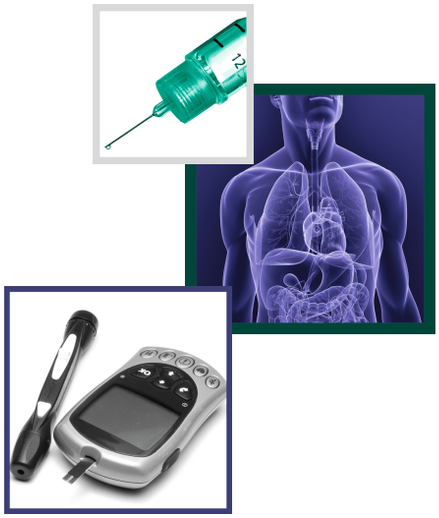
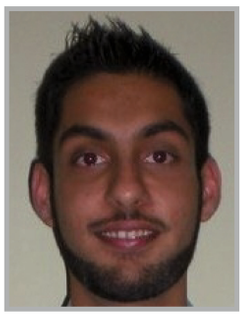
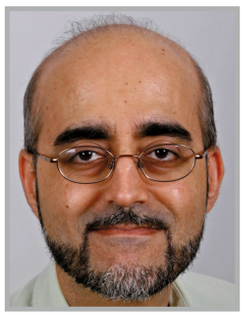
EDITORIAL



Does androgen deprivation therapy increase diabetes risk?





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Prostate cancer is the second most common cancer in men worldwide, and accounted for over one in seven new cancer diagnoses in Canada in 2011 [1]. Owing to increased screening, the incidence and prevalence of prostate cancer continue to rise. In men with locally advanced or high-risk localized disease as well as metastatic disease, one of the most common treatments is androgen deprivation therapy (ADT) [2], since it has shown to improve both disease-specific-survival and overall survival as well as quality of life [3,4]. However, ADT has also been associated with many side effects, including an increased risk of diabetes [3].

Androgen deprivation for treating prostate cancer is based on the fact that androgens play a role in stimulating prostate tissue growth and proliferation. Androgen deprivation can be performed in multiple ways; either medically (with gonadotropin releasing hormone (GnRH) agonists or GnRH antagonists with or without antiandrogens, which block testosterone action at the receptor level) or through surgery (bilateral orchiectomy), which involves removal of the testicles. Below we review several lines of evidence demonstrating a link between ADT use and diabetes, along with putative mechanisms.

A number of retrospective studies using administrative databases have demonstrated a link between ADT use and diabetes. The earliest study to show this link was carried out by Keating *et al.* in a retrospective longitudinal claims-based study in 2006 involving over 73,000 patients [5]. The authors found that GnRH use was associated with an increased incidence of diabetes as well as other cardiovascular diseases (hazard ratio: 1.44; $p < 0.001$). Using a similar approach with province-wide data, our group found an increased risk of diabetes after a median follow-up of 6.5 years among 19,079 ADT users compared with controls (hazard ratio: 1.16; 95% CI: 1.11–1.21) [6]. This translated into an excess risk of developing diabetes of 1.1% over 6.5 years. This translates into a number needed to harm of 91 over 6.5 years, such that for every 91 men treated with ADT for a median of 6.5 years, one patient would develop diabetes. These studies, although featuring large sample sizes, are limited primarily by

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their retrospective nature and use of administrative data, which often lack important clinical details such as family history, BMI and blood glucose levels.

Several small case–control studies have examined the link between ADT use and metabolic parameters. Dockery *et al*. performed a case–control study comparing 16 patients undergoing ADT with 15 controls and found an increase in serum insulin levels in the ADT group over a 3-month period of androgen suppression, while no increase in serum insulin was observed in the control group [7]. A study conducted by our group recruited 75 patients with prostate cancer, 38 of whom underwent ADT [8]. Patients were followed for 12 months after starting treatment. After excluding patients with prior diabetes, we found that ADT users had a significantly higher 12-month fasting glucose level compared to controls [8]. These results support the link between androgen deprivation and risk for diabetes, this is likely to be due to insulin resistance mechanisms.

Since higher fasting glucose levels in adults are directly correlated with an increased risk of developing Type 2 diabetes mellitus, it can be assumed that patients who undergo ADT have a higher risk for developing diabetes. Although many short-term studies have demonstrated that ADT can increase insulin resistance as early as 3 months into therapy, it is also apparent that the duration of androgen deprivation is directly linked to worsening glycemic control. A long-term study conducted by Basaria *et al*. enrolled 18 patients undergoing long-term ADT (for at least 12 months), none of whom had prior diabetes. After factoring in age, serum insulin levels, fasting glucose and duration of ADT treatment, they found that the degree of insulin resistance and hyperglycemia were directly related to the duration of ADT [9].

In addition to nondiabetic men starting ADT being at risk for developing diabetes, patients who already have diabetes who undergo ADT are at risk of worsening glycemic control. A study conducted by Haidar *et al*. following 29 patients with insulin-requiring diabetes mellitus undergoing ADT for 2 years demonstrated that glycemic control worsened substantially in all patients, with patients showing an increasing fasting glucose level as well as an increase in insulin requirements [10].

There may be multiple mechanisms that cause patients on ADT to be at increased risk for insulin resistance, and therefore diabetes. The most obviously implicated pathway is via (central) obesity. There is much evidence that ADT causes an increase in body fat and decreased muscle mass [11]. For example, a study by Smith *et al*. found an 11% increase in body fat mass from the time of initiating ADT to 12 months after starting therapy [12]. This observation has been confirmed by numerous other authors, who have demonstrated varying levels of increased body fat levels within 3–12 months of ADT initiation [11–15], and is thought to be secondary to profound hypogonadism. It is unclear whether the weight gain causes insulin resistance or *vice versa*, since hyperinsulinemia can cause a state of anabolism leading to increased fat deposition. However, regardless of the root cause, an increase in body fat coupled with insulin resistance can lead a patient on a vicious cycle that can ultimately lead to diabetes and other comorbidities. Many men on ADT also engage in limited physical activity because ADT leads to both muscle atrophy and fatigue. Restrictions in physical activity likely aggravate the excess adiposity and insulin resistance from hypogonadism.

So how do these findings translate into clinical practice? As previously explained, a great deal of research supports increased body fat and insulin resistance with ADT. The implications of this are significant; men undergoing ADT are 1.26 times more likely to develop diabetes than men with prostate cancer undergoing other forms of treatment [6]. Thus, patients with prostate cancer who opt to undergo ADT should be advised of this side effect of therapy and regularly monitored for signs of insulin resistance and diabetes. Although there are no formal guidelines for monitoring at this point in time, we suggest a baseline fasting blood glucose at time of initiation of ADT, and yearly monitoring thereafter. Monitoring bodyweight and waist circumference regularly is also reasonable. Since there is no reason to believe that this cancer population is any different from the general population in terms of preventative measures, it makes sense to counsel patients on weight reduction, exercise and healthy eating habits to help prevent insulin resistance [16]. Exercise may have several other benefits for this population of patients, including avoiding or reversing muscle loss, improving quality of life and decreasing fatigue [17]. Metformin or glitazones may also be prescribed if necessary to help lower blood glucose levels and prevent diabetes [18,19], although neither of these drugs have specifically been studied in men

on ADT. Ultimately, patients have to be aware that this potentially life-saving treatment comes with side effects, and they should be empowered to take control of their health to aid them in avoiding complications of toxic cancer therapy, such as diabetes. At the same time, physicians and patients should recognize that the absolute risk of developing diabetes from ADT is relatively low, and several preventive manoeuvres can be undertaken to reduce this risk.

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