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Induced testosterone deficiency: from clinical presentation of fatigue, erectile dysfunction and muscle atrophy to insulin resistance and diabetes

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Abstract

Over the past 60 years, androgen deprivation therapy has been the mainstay of treatment of metastatic prostate cancer. However, research findings suggest that androgen deprivation therapy inflicts serious adverse effects on overall health and reduces the quality of life. Among the adverse effects known to date are insulin resistance, diabetes, metabolic syndrome fatigue, erectile dysfunction, and cardiovascular disease. In this clinical perspective, we discuss the relationship between induced androgen deficiency and a host of pathologies in the course of treatment with androgen deprivation therapy for prostate cancer patients.

Keywords: androgen deprivation therapy; fatigue; insulin resistance; mitochondria; mitochondrial dysfunction; testosterone; testosterone deficiency; type 2 diabetes.

Introduction

Over the past 60 years, androgen deprivation therapy has been the mainstay of treatment of metastatic prostate cancer. However, research findings suggest that androgen deprivation therapy inflicts serious adverse effects on overall health and reduces the quality of life. Among the adverse effects known to date are insulin resistance [1, 2], diabetes [3–10], metabolic syndrome [11–13], fatigue [14–17], sexual dysfunction [18–21], and cardiovascular disease [16, 22–25]. In this clinical perspective (Part 1), we discuss the relationship between induced androgen deficiency and a host of pathologies in the course of treatment with androgen deprivation therapy for prostate cancer patients.

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Case study and clinical perspective of androgen suppression in a man with advancing prostate adenocarcinoma

This case illustrates the rebounding symptoms of "fatigue" erectile dysfunction, strength loss, muscle wasting, insulin resistance, and finally hyperglycemia with diabetes in a 56-year-old man with progressive prostate cancer. The treatment of his advancing prostate cancer involved intermittent androgen suppression (IAS) with a total of 12 cycles of androgen deprivation for a period of 13 years (1995–2008) before he died of recurrent colon cancer. By the seventh cycle of androgen suppression, he developed glucose intolerance and fasting blood sugars in the range between 130 and 240 mg/dL, (7.2–13.3 mmol/L) but because of the IAS program, he never required medical treatment of his fluctuating hyperglycemia.

At age 43 years, he was first diagnosed to have localized prostate cancer Gleason score 7 (4+3, 3+4) with a prostate specific antigen (PSA) level of 13.5 ng/mL. Both computed axial tomography (CAT) and bone scans were negative. After the first androgen suppression treatment with 7.5 mg lupron, the PSA decreased to 0.032 ng/mL and a mutual decision was made to proceed with a radical prostatectomy. The pathology confirmed prostate cancer with right seminal vesicle invasion without lymph node involvement. Because of the profound "fatigue and strength loss" from his first lupron injection preoperatively, he and his physician mutually agreed to use IAS to manage his prostate cancer.

His description of the predictable event of profound fatigue is characterized as follows: "After the lupron injections, I get the 'hot flashes and sweating' and within 7–10 days, I become so tired and incapacitated such that I cannot not do the chores and work at the farm and the contracting business. I lost my libido and spontaneous erections about the same time. I still had muscles and I looked good but I could barely move around the house let alone the farm. By the end of the third week, I couldn't lift heavy machines like before and my sons had to help me."

His wife described him as a sudden "couch potato" and does not want to do anything except to sleep. The patient noted that "I can always tell when things are going to get better, when I wake up with some penile erections and would start to think more about sex and then the strength comes back about a week later."

From 1995 to 2008, a period of 13 years, he underwent 12 cycles of androgen suppression. Whenever his PSA dropped to below 3 ng/mL, we stopped the therapy (off period) and restarted when the PSA was ≥10 ng/mL (on period). As

expected, the intervals between androgen suppression (on periods) became shorter until the last two cycles when the PSA started to increase to 300 ng/mL. He later developed clinical diabetes by his seventh cycle of therapy.

What was clearly noticeable was that this robust man would become fatigued within 10 days to 2 weeks after androgen suppression. He would lose his libido immediately with onset of hot flashes within 2 days, his penis "would shrink," with no morning erections ("penis fatigue"), but there was no evidence of skeletal muscle loss or anemia at the time. The feeling of being "tired" by 10 days and the eventual loss of muscle strength by 4 weeks were easily noticeable, yet by outward appearance, he looked fine.

His wife noted that within 1 week, he showed lack of energy to manage his farm estate or his businesses, and showed no interest in horseracing nor in casinos – in essence, he became a different person plagued with fatigue. After 3 months of androgen suppression, this man will first notice morning erections and less fatigue, signifying a return of his androgen production and then later an increase in muscle strength and endurance. He later developed visceral abdominal fat with shoulder and thigh muscle wasting, and never returned to his preoperative physical appearance. His blood sugar level would return to within the reference range in the androgen off periods and would increase to range of 180–240 mg/dL (10–13.3 mmol/L) during the androgen suppression periods. He monitored his blood sugar levels and modified his diet and carbohydrate intake.

Androgen suppression as treatment for advanced prostate cancer

Urological surgeons and oncologists are all too familiar with this scenario of men who have undergone androgen ablation to arrest their metastatic, progressive, and aggressive prostate cancer. From 1940s to the 1980s, surgical castration was the standard of treatment for advanced metastatic prostate cancer before the discovery of the luteinizing hormone-releasing hormone (LHRH) agonists and its subsequent use as an alternative form of androgen suppression. Today, the social stigma of human castration for medical conditions carries a "demasculinization image" such that chemical ablation or suppression has become more socially acceptable even though the results are similar. The testosterone levels decrease from an average of 500 ng/dL to castrate levels of 30 ng/dL or lower. Additional anti-androgen medication is added to suppress the effect of adrenal androgen production.

For prostate cancer patients with metastatic progressive cancers, androgen suppression therapy will immediately result in relief of pain from bone metastasis, spinal cord compression, and decrease in hydronephrosis from ureteral obstruction or prostate outlet obstruction, as well as in an immediate decrease in serum PSA levels. Androgen hormonal suppression is not curative but only palliative, as the period of efficacy is at best 5–7 years before further progression of the hormone-resistant prostate cancer leads to eventual death. Yet, hormonal suppression therapy is the most effective medical intervention for metastatic prostate cancer over any other forms of cytotoxic therapy or immunotherapy.

The late W.W. Scott, who worked under Charles Huggins at the University of Chicago and was formerly Chief of Urology at Johns Hopkins, was involved with numerous studies on hormonal treatments for metastatic prostate cancer such as the National Prostatic Cancer Study and the Veterans Administration Cooperative Study in the 1970s. In 1978, he once reflected that surgical or medical castration may be the best "human model of abrupt andropause seen ordinarily in aging men diffused over a 50-year period to their time of death. We will not only know why testosterone depletion arrests prostate cancer progression but also learn about the metabolic consequences with androgen ablation." As total hysterectomy results in woman's abrupt menopause, androgen suppression and surgical castration leads to abrupt changes in men. Both develop "hot flashes" and a whole complex of associated symptoms and new medical problems. For men, the lack of testosterone leads to fatigue, sexual dysfunction, muscle loss, osteoporosis, and anemia as part of the clinical picture; however, today, we know that testosterone deficiency leads to changes in cellular and biochemical metabolism resulting in insulin resistance [26–31] and physiological changes of skeletal cells as well as smooth muscle abnormalities [32, 33] leading to penile erectile dysfunctions and cardiovascular changes [33–36].

Relationship between low testosterone levels and glucose metabolism

In 2008, an article entitled "Androgen deprivation therapy, insulin resistance, and cardiovascular mortality: an inconvenient truth" made urologists, oncologists, and endocrinologists aware of the adverse effects of chemical castration, which must be weighed against the benefits in controlling prostate cancer [1, 22]. By 6 months, there is insulin resistance and by 9 months, glucose tolerance abnormalities with cardiovascular disease [1, 22].

Most urologists and oncologists reserve total androgen suppression as the treatment of choice for men with aggressive and progressive metastatic prostate cancer but not for men with stable localized cancer. There is a growing emergence of clinicians and patients who choose intermittent androgen suppression therapy (IAS) to decrease the adverse effects over the traditional continuous androgen suppression for advanced disease, as studies comparing these two approaches show no difference in survival but a definite improvement in decreasing the adverse effects [37, 38]. The understanding of testosterone's relationship with metabolism and mitochondrial dysfunction was gleaned from studies in animal models and clinical studies showing a correlation from basic science research to longitudinal clinical studies.

This will be further discussed in Part 2 of this two-part series. Marin and Bjorntorp's group clearly showed that testosterone, not 5α-dihydrotestosterone, regulated glucose metabolism by using a unique assay of hyperinsulinemic euglycemic clamp analysis with more sensitivity to detect insulin resistance and glucose disposal rate into muscle in animal

and human studies. What is most remarkable was the reversal back to normal insulin sensitivity within 48 h after repletion of testosterone in the animal studies. This quick response suggests that this effect may be a non-genomic testosterone effect [39, 40]. This will be further discussed in Part 2 of this two-part series.

Mauras et al. [41] carried out biochemical and physiological studies in six 23-year-old men in which chemically inducing acute testosterone deficiency from baseline levels of testosterone 500 ng/dL down to 30 ng/dL led to decrease in strength, loss of muscle mass, and increased adipose tissues. Quadriceps extension strength decreased to about 50% within a period of 10 weeks. There was evidence of decreased fat oxidation and decreased total protein synthesis in all subjects.

Pitteloud and associates [26–28] generated much discussion about the role of testosterone as a modulator of glucose metabolism, oxidative phosphorylation, and mitochondrial dysfunction. In April 2005, the first investigation of insulin resistance utilized a more sensitive method to measure glucose metabolism [27, 28] than the traditional glucose tolerance test by "hyperinsulinemic and euglycemic clamp," the same method of Bjorntorp's group in Sweden [42, 43], in which 18 men first underwent chemical castration by treatment with a gonadotrophin-releasing hormone (GnRH) antagonist and then reintroduced GnRH and human chorionic gonadotropin (HCG) to induce testicular production of testosterone [27, 28]. The increase in testosterone production correlated positively with insulin sensitivity, showing that the greater the testosterone production, the more likely the patient will be insulin sensitive. Another study published in July 2005 showed that hypogonadal men were less insulin sensitive, with higher fasting glucose and higher insulin levels [27, 28]. The study also showed a decrease in oxidative phosphorylation and changes in maximal oxygen uptake (VO_2) consistent with mitochondrial dysfunction [27, 28].

Today, urologists and oncologists use androgen suppression as the first line of therapy for metastatic prostate cancer, and acknowledge the adverse effects as a price to pay for cancer arrest in exchange for their "quality of life." Hot flashes, fatigue, erectile dysfunction, muscle mass loss with fat gain with gynecomastia, depression, and cognitive decline are a symptom complex measured in scales of severity but not explained by physiological alterations.

Are fatigue, loss of strength, and erectile dysfunction symptoms of early changes in intracellular pathways and dysfunction in muscle cells?

Upon castration or androgen suppression, among the numerous complexes of patient symptoms, the immediate onset of fatigue and loss of strength stand out as the most consistent symptoms occurring within a 2- to 4-week period, and all occur long before the onset of muscle mass loss or anemia. Although we have a scoring system for "fatigue," we still do not have a physiological, cellular, or biochemical explanation for fatigue and strength loss. We categorize these symptoms along with depression with mood swings, cognitive changes, and erectile dysfunction as part of the generalized "quality of life" issues and segregate them from the more physiological and biochemical findings of osteoporosis, anemia, and muscle loss and adiposity as the "real metabolic and anatomical changes."

Changes in glucose metabolism results from mitochondrial dysfunctions and mitochondrial biogenesis (number of active mitochondria). Since we know that mitochondrial dysfunctions are present in individuals prone to insulin sensitivity, could it be that symptoms such as fatigue imply early cellular changes in energy metabolism in mitochondria? In the human model of acute androgen suppression in castrated men with advanced prostate cancers, could fatigue, erectile dysfunction, and muscle strength loss be results of mitochondrial dysfunction? Could this process be part of a spectrum of events in mitochondrial dysfunctions that later progresses to metabolic alterations leading to insulin resistance, glucose intolerance, and finally to overt clinical diabetes? Fatigue and erectile dysfunction occur simultaneously soon after androgen suppression in these men.

Animal studies provide evidence that there may be a unifying theory of androgen deprivation resulting in histological changes and underlying mitochondrial abnormalities [33, 44, 45]. Classic animal studies looking at the physiological, biochemical, histological, and electron microscopic findings of corporal penile smooth muscle changes with surgical castration show histological muscular atrophy and "vacuolization" within cells with "mitochondrial swelling" within 3 weeks after castration. Replacement with testosterone in castrated rabbits restores the original normal anatomy and functions. This aspect will be discussed further in Part 2 of this two-part series. There is also evidence of accumulation of adipocytes adjacent to atrophied smooth muscle cells. Testosterone may affect the mitochondrial functions within the smooth muscle cells of vascular tissues as well as of the neural tissues innervating the corporal bodies of the penis [33, 44–48].

Fatigue: other models for study and comparison

As there is no clear scientific research in the literature on the subject of fatigue from either androgen suppression or from testosterone deficiency, we must look elsewhere to learn and piece together a cellular and biochemical explanation for "fatigue." One model of cellular changes from fatigue involves HIV patients exposed to drug treatment side effects. Nucleoside analogues, such as stavudine are effective drugs against virus infection, but they also induce a toxic effect on mitochondria by inhibiting human DNA polymerase γ, thereby worsening the symptom "fatigue complex" in HIV-infected patients. Recent advancements show that patients using such drugs had decreases of 68% in mitochondrial DNA/nuclear DNA ratio in red blood cells and muscle cells compared to normal healthy men without disease and 43% less mitochondrial DNA/nuclear DNA ratio than the group of HIV-infected men without symptoms. The toxic effect on mitochondria leads to an aberration of glycolysis resulting in an inefficient

utilization of pyruvate in the aerobic Krebs cycle pathway shifting to an anaerobic pathway leading to higher production of lactic acid [49]. The fatigue symptom seen in HIV-positive men treated with a nucleoside analogue was correlated to the level of fatigue.

Historically, it is well known that as much as 50% of HIV-infected men have low testosterone levels [50]. Rabkin et al. [51] investigated fatigue in HIV-positive men in a randomized double-blind study and clearly showed that men receiving testosterone treatment showed a marked improvement in problems with fatigue compared to the placebo and fluoxetine arms. They used the Chalder fatigue scale to measure fatigue levels.

In 2008, Bhasin's group examined 60 men with HIV infection with low testosterone levels of <400 ng/dL and evaluated them for a number of parameters in a randomized study and treated one group with supraphysiological doses of 300 mg of testosterone enanthate intramuscularly, weekly for 16 weeks or 4 months [52]. The patient in this study had a special category of "fatigability" along with changes in muscle strength. Both parameters showed significant improvement at the end of the study. Fatiguability was defined as repetition of leg presses. This study suggests that testosterone may have some direct effect on fatigue and muscle strength [52, 53].

Discussion

When androgen suppression is implemented as treatment for men with prostate cancer, the sequence of symptoms and physiological changes are predictable, starting with rapid onset of severe fatigue, muscle strength loss, and erectile dysfunction, followed by the slower changes of muscle wasting and visceral fat accumulation with gynecomastia, osteoporosis, and anemia. This phenomenon is repeatedly seen in the prostate cancer patient presented above, who elected to use IAS where symptoms fluctuated from the extremes of total chemical androgen suppression to normalization of androgenization in the off period. The return of morning erections, signifying penile corporal smooth repletion, seems to occur simultaneously with less symptoms of fatigue and revitalization of muscle strength as the endogenous production of testosterone increases in the off periods. As the patient put it, "When penile fatigue is gone, I know I'm going to feel better!"

Just as quickly as men undergoing androgen suppression present with the complex of symptoms noted above, we see an even more dramatic change on the other extreme where supraphysiological doses of injectable testosterone replacement in young men with testosterone deficiency show immediate response [52, 53].

Within a short duration of subcutaneous injection of a supraphysiological dose of testosterone cypionate (200–400 mg) to the subject, we observed an impressive change from a person with severe fatigue, slow motor movements, and depression to one with a new tempo of energy, vigor, and mental alertness. Moreover, within a few weeks of testosterone replacement therapy, increased libido and erections were also noted. This turnaround time is much too quick to be explained by a genomic effect and long before the patient gains muscle mass or recover from anemia. This suggests that there must be a non-genomic, fast-acting effect of testosterone yet to be fully understood. This effect will be further discussed in Part 2 of this two-part series. It could be that the initial presentation of severe fatigue can be attributed to a non-genomic mitochondrial dysfunction involving altered oxidative phosphorylation and later leading to a dysfunction of glucose metabolism and finally to overt metabolic disorder of diabetes.

Basaria [1] noted that within 6 months of androgen suppression, one can see insulin resistance and by 9 months, evidence of abnormal glucose intolerance with early diabetes. The second part of this two-part series will elaborate on the histological, cellular, and biochemical changes associated with testosterone deficiency leading to a unifying hypothesis of intracellular mitochondrial dysfunctions as a basis of the spectrum of symptoms from fatigue and erectile dysfunction and strength loss to insulin resistance and diabetes and finally to cardiovascular disease.

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