REVIEW

Prostate Cancer and Metabolic Syndrome: Is there a link?

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Abstract

Metabolic syndrome has become quite prevalent within our society. Over the past two decades, the prevalence of metabolic syndrome has sharply increased worldwide and it has become a major public health problem in several countries. It is associated with the global epidemic of obesity and diabetes mellitus and imposes numerous cardiovascular risks. Prostate cancer is the second most common cancer among men, surpassed only by non-melanoma skin cancer. A considerable body of evidence exists suggesting that some components of the metabolic syndrome have been associated with the risk of prostate cancer. These components include obesity, an abdominal fat distribution, and hyperinsulinemia. Androgen deprivation therapy (ADT) is the most widely used therapeutic modality in prostate cancer. It changed the body composition and lipid profile of men with prostate cancer. Androgen deficiency is associated with increased levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, increased production of proinflammatory factors, and increased thickness of the arterial wall and contributes to endothelial dysfunction. The aim of this review is to evaluate the association between metabolic syndrome and prostate cancer and to discuss the implications of androgen deficiency in men with cardiovascular risk factors. A comprehensive literature search was carried out with the use of PubMed from 1980 through 2011, and relevant articles pertinent to metabolic syndrome and prostate cancer are evaluated and discussed.

Key words: Metabolic syndrome - prostate cancer - hyperlipidemia - androgen deprivation - vitamin D

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Introduction

Prostate cancer is the second most common cancer among men, surpassed only by non-melanoma (Reis et al., 2009; Gugliotta et al., 2008). It is the most common non-cutaneous cancer and the second leading cause of cancer death among men in the United States of America (Powell, 2007). An estimated 186,320 American men received a new diagnosis of prostate cancer in 2008 (National Cancer Institute Surveillance Epidemiological and End Results Program, 2009) and the incidence of this disease is estimated to exceed 192,000 cases in 2009 (Jemal et al., 2008)

Despite the high morbidity associated with prostate cancer, the only established risk factors are age, race, and a family history (Hsing and Chokkalingam, 2006). However, large geographic variation in prostate cancer risk suggests that lifestyle related factors, such as westernization along with genes and dietary factors are believed to contribute to the development of this disease (Gro¨nberg, 2003; Nelson et al., 2003). Men in westernized countries have incidence rates that are 10- to 15-fold those of Asian men (Hsing and Devesa, 2001) although prostate cancer incidence in low-risk Asian countries has risen rapidly in recent years (Park et al., 2006; Hsing et al., 1998). African-American men have an approximately 1.6-fold greater chance of being diagnosed with prostate cancer when compared with Caucasian men and a 2.4-fold greater chance of dying from the disease (Jemal et al., 2006).

Over the past two decades the prevalence of metabolic syndrome has been increasing worldwide and it has become a major public health problem in several countries (Hsing et al., 2000; Malik et al., 2004). It is an emerging clinical problem of enormous proportions, and is associated with the global epidemic of obesity and diabetes mellitus (Laaksonen et al., 2002). The metabolic syndrome is a common clinical condition in countries with a high incidence of obesity and western dietary patterns. It is difficult to properly diagnose, because its presentation varies according to the different components that constitute the syndrome (Laaksonen et al., 2002). Its etiology is complex and comprises multiple factors, including excess weight and a sedentary lifestyle coupled with high-energy intake, and unknown genetic factors (Reaven, 1988; Laaksonen et al., 2002).

Metabolic syndrome is considered an emerging hypothesis in the etiology of prostate cancer. A number of studies have found that features of the metabolic syndrome may be predictive of prostate cancer risk. This review aims to summarize the latest findings on the association between metabolic syndrome and prostate cancer. This review also evaluated recent studies on (i) the adverse effects of ADT in men with prostate cancer such as dyslipidaemia, increased peripheral insulin resistance,

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and the development of metabolic syndrome and (ii) the implication of factors related to the metabolic syndrome and low levels of vitamin D in prostate cancer risk.

Metabolic Syndrome

In Europe, the reported prevalence of the metabolic syndrome in middle-aged men ranges from 7% to 36% (Lakka et al., 2002; Balkau et al., 2002). The prevalence of the metabolic syndrome was 26.7% among adults in the United States of America in the 1999-2000 National Health and Nutrition Examination Survey (NHANES) (Ford et al., 2004). In a more recent study, approximately 35% to 39% of the adult population in the United States of America has metabolic syndrome with similar rates in men and women (Golden et al., 2009).

The metabolic syndrome is characterized by a cluster of biochemical abnormalities and associated clinical conditions, not all of which are necessarily present in a given case, but which include altered glucose metabolism and insulin bioactivity resulting in hyperglycemia, hyperinsulinemia, dyslipidemia [low levels of high density lipoprotein (HDL)-cholesterol and hypertriglyceridemia], hypertension, and type 2 diabetes mellitus (Ford et al., 2002). Other components of metabolic syndrome include prothrombotic and proinflammatory states (Grundy et al., 2004). Central obesity is often present, but the syndrome does occur in its absence. Lean individuals exhibit a wide range of insulin sensitivity, and may have levels as low as those of obese insulin-resistant subjects (Kahn et al., 2001).

Metabolic syndrome is a cluster of risk factors for type 2 diabetes mellitus and cardiovascular disease (CVD), and is associated with increased mortality from these and other conditions (Isomaa et al., 2001; Trevisan et al., 1998). In a study by Sattar et al. (2003), males with four or five features of metabolic syndrome [using a modified National Cholesterol Education Program (NCEP) definition], compared with those with none, had a 3.7-fold increase in coronary heart disease (CHD) and a 24.5-fold increase in type 2 diabetes mellitus. In a prospective cohort study of 6,255 subjects 30 to 75 years, the risks of all-cause mortality as well as death from CHD and CVD were also elevated (Malik et al., 2004). Wilson and colleagues noted that more than any three the following including elevated systolic blood pressure (SBP), elevated body mass index (BMI), elevated serum glucose, elevated triglycerides or low HDL-cholesterol were associated with more than double the risk for coronary artery disease (CAD) (Wilson et al., 1999).

Numerous definitions of metabolic syndrome have been proposed by various organizations, including the American Association of Clinical Endocrinologists (AACE), European Group for the Study of Insulin Resistance (EGIR), International Diabetes Federation (IDF), the NCEP Adult Treatment Panel III (NCEP ATP III), and the World Health Organization (WHO). Each of the definitions shares many similarities, including the presence of criteria relating to dyslipidemia, hyperglycemia, hypertension and obesity. However, several differences among the classifications are noted. The laboratory values that define these aforementioned criteria and the number of positive criteria necessary to be classified as having metabolic syndrome vary among the organizations. Additionally, the AACE, EGIR, IDF and WHO require the presence of certain criteria such as evidence of central obesity, hyperinsulinemia or insulin resistance to fulfill their classification of metabolic syndrome, whereas the NCEP ATP III lacks this constraint. The NCEP ATP III definition is the one most used today because it incorporates the key concepts of metabolic syndrome, relies on commonly used laboratory studies available to most physicians, and is less restrictive than the other classifications (Huang, 2009).

According to the NCEP ATP III, individuals who possess at least three of the following five features are classified as having metabolic syndrome: (1) abdominal obesity (waist circumference of >102 cm in men or >88 cm in women), (2) hypertriglyceridemia (≥150 mg/dL), (≥1.70 mmol/L), (3) low HDL-cholesterol (< 40 mg/dL) (<1.03 mmol/L) in men and (< 50 mg/dL) (< 1.29 mmol/L) in women, (4) high blood pressure (≥130/85 mmHg) or

Table 1. Association Between Metabolic Syndrome and Prostate Cancer Risk in Studies Performed in Different Countries

Studies/Authors	Country	Summary of findings
Beebe-Dimmer et al., 2007	United States of America	Features of the metabolic syndrome, specifically abdominal obesity and hypertension, are associated with prostate cancer in African-American men.
Beebe-Dimmer er al., 2009	United States of America	The metabolic syndrome was associated with prostate cancer risk in African-American men.
Laukkanan et al., 2004	Finland	Middle-aged men with the metabolic syndrome were more likely to develop prostate cancer.
Lund Haheim et al., 2006	Norway	The metabolic syndrome was found to predict prostate cancer, indicating an association between insulin resistance and the incidence of prostate cancer.
Martin et al., 2009	Norway	There was little evidence that the features of metabolic syndrome were associated with incident or fatal prostate cancer
Wallner et al., 2011	United States of America	The metabolic syndrome was only minimally and inversely associated with prostate cancer.
Tande et al., 2006	United States of America	Men with the metabolic syndrome (≥3 components) were significantly less likely to develop prostate cancer.

pharmacological treatment for hypertension and (5) high fasting blood glucose (≥ 110 mg/dL) (≥ 6.1 mmol/L) (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001).

The IDF defines the metabolic syndrome as established if the absolute criterion abdominal obesity (waist circumference greater than the reference values) is present and at least two of the following: (1) fasting plasma glucose level ≥ 100 mg/dL (≥ 5.6 mmol/L) or pharmacological treatment for type 2 diabetes mellitus, (2) arterial hypertension (≥ 130/85 mmHg) or pharmacological treatment for hypertension, (3) elevated triglyceride level (150 mg/dL) (≥ 1.70 mmol/L) and/or pharmacological treatment for this lipid abnormality or (4) decreased HDL-cholesterol level (< 40 mg/dL) (< 1.03 mmol/L) in men or (< 50 mg/dL) (< 1.29 mmol/L) in women or pharmacological treatment thereof (International Diabetes Federation, 2005).

Prostate Specific Antigen and Metabolic Syndrome

The prostate specific antigen (PSA) test is used worldwide as a screening tool, as part of the diagnostic workup to rule out prostate cancer, and in the management of this disease after diagnosis. A randomized European study showed that PSA-based screening reduced the rate of death from prostate cancer by 20% (Schröder et al., 2005). The PSA levels may be affected by factors such as age, prostate volume and obesity, and the sensitivity and specificity of the PSA test has been questioned (Freedland et al., 2006; Kim et al., 2007; Chun et al., 2007). Approximately 1.5 million American men ages 40 to 69 years have PSA levels of > 4.0 ng/mL, a widely used cut-off value for a positive screening result (Schröder et al., 2005). However, there are concerns about the lack of specificity of the PSA test as many men with PSA < 4.0 ng/mL have prostate cancer. The accuracy of PSA test interpretation can be improved by controlling factors such as age, prostate volume, and ethnicity (Hernández and Thompson, 2004).

Metabolic syndrome is considered an emerging hypothesis in the etiology of prostate cancer, and some metabolic risk factors are associated with serum PSA levels. Several studies have examined the association between various metabolic risk factors and PSA level (Parekh et al., 2008; Rundle and Neugent, 2008; Werny et al., 2006). A study by Kim et al. (2008) in investigating the association of metabolic syndrome and serum PSA level in a group of 2,007 men (aged 30 to 79 years) without prostate cancer, found that the prevalence and sum of metabolic syndrome components were inversely associated with serum PSA levels. Multivariate analysis showed that serum PSA levels were strongly associated with abdominal obesity and impaired fasting glucose levels (Kim et al., 2008).

Studies have reported that obesity was associated with decreased PSA levels and an enlarged prostate volume may decrease the sensitivity of prostate biopsy, perhaps leading to delay in the detection of prostate cancer (Baillargeon et al., 2005; Kristal et al., 2006). The lower PSA level in obese men is due to obesity-related hemodilution or the decrease in circulating androgens found in obese men (Kristal et al., 2006; Bañez et al., 2007; Grubb et al., 2009).

Obesity and insulin resistance are principal components of metabolic syndrome that cause other metabolic abnormalities (Haffner and Taegtmeyer, 2003). Obesity is related to endocrine and metabolic changes, and obese men have elevated levels of estrogen, insulin-like growth factor 1 (IGF-1) and insulin levels, and decreased testosterone levels (Moyad, 2002). Hyperinsulinaemia has been shown to have a direct effect on the liver, suppressing the production of sex hormone-binding globulin (SHBG) and insulin-like growth factor-binding proteins 1 and 2 (IGFBP-1, -2) while stimulating the production of IGF-1 (Barnard et al., 2002). Metabolic syndrome is believed to affect the production of PSA through these metabolic activities that arise due to the presence of obesity and insulin resistance.

Jeong et al. (2010) investigated the association of metabolic syndrome and its metabolic components with serum PSA levels in a large screened population of 26,726 Asian men ages 40 years or older without a history of prostate cancer. They found that although mean PSA levels were lower in men with metabolic syndrome than in those without the condition, serum PSA was not associated with metabolic syndrome. Among metabolic risk factors, waist circumference and fasting blood glucose levels were inversely correlated with serum PSA, whereas blood pressure was positively correlated. These associations remained significant after adjusting for age, BMI, and other metabolic risk factors (Jeong et al., 2010). According to Jeong et al. (2010) the lack of association between metabolic syndrome and serum PSA may reflect the heterogeneous relationship between each metabolic risk factor and serum PSA. In the contrary, Rundle et al. (2009) found that waist circumference was positively associated with PSA level, even after controlling for BMI. The association of BP with serum PSA levels remains controversial. Parekh et al. (2008) reported that elevated DBP, but not SBP, was associated with elevated serum PSA. Conversely, a NHANES study conducted in the United States of America found that high BP was not associated with serum PSA level (Werny et al., 2006). The conflicting relationship reported in the literature might have resulted from the differences in study sample size, the inclusion criteria for study subjects (age and ethnicity), and the definition of hypertension (cut-off point of hypertension and information about antihypertensive medication).

Metabolic Syndrome and Prostate Cancer

Metabolic syndrome is thought to play a role in the etiology of prostate cancer. Several groups of investigators have suggested that features of the metabolic syndrome may be predictive of prostate cancer risk. Few studies have considered the full metabolic syndrome. Studies in Scandianvians (Lund Håheim et al., 2006; Laukkanen et al., 2004) and in African Americans (Beebe-Dimmer et al., 2007; Beebe-Dimmer et al., 2009) have found a positive

association, while others found an inverse association in a mixed population (Tande et al., 2006) or no relationship in Scandinavians (Martin et al., 2009) or Caucasians in the United States of America (Hsing et al., 2000) (Table 1).

Lund-Håheim et al. (2006) studied modified components of the metabolic syndrome according to NCEP ATP III criteria in a prospective cohort of 16,209 men aged 40-49 years who participated in the Oslo Study, followed up for 27 years. Men with measured values that placed them in the upper quartile for any two features of the metabolic syndrome were 23% more likely to be diagnosed with prostate cancer. Men who exhibited any three features were 56% more likely to be diagnosed prostate cancer compared with the rest of the cohort. The weak associations between insulin resistance and the incidence of prostate cancer may be due to this cohort being young (Lund Haheim et al., 2006). Beebe-Dimmer et al. (2009) conducted a case-control study (637 patients and 244 controls) to test the association between metabolic syndrome features and prostate cancer. African-American men constituted 43% of the study population (Beebe-Dimmer et al., 2009). Metabolic syndrome, defined using a modified version of the NCEP ATP III criteria, was marginally associated with an increased risk of prostate cancer in African-American men [odds ratio (OR) 1.71], but not in Caucasian men (OR 1.02). African-American men with organ-confined disease were more likely to have a history of metabolic syndrome than were the controls (OR 1.82). No association was observed among those with advanced-stage disease (OR 0.93).

However, there are studies that do not uniformly suggest that metabolic syndrome is important in prostate carcinogenesis. An inverse relationship between metabolic syndrome and prostate cancer risk was reported in a large cohort of men participating in the Atherosclerosis Risk in Communities (ARIC) study comprising 6,429 men in four United States of America communities initially with no history of cancer and aged 45-64 years. The authors reported that men with the metabolic syndrome (three or more components) were significantly less likely to develop prostate cancer (RR = 0.77) than men without the metabolic syndrome (Tande et al., 2006). The Flint Men's Health Study (FMHS), a community-based, case-control study was the first study of metabolic syndrome features and prostate cancer conducted exclusively in a population of African American men (Beebe-Dimmer et al., 2007). The men with prostate cancer also were more likely than their control counterparts to exhibit metabolic syndrome characteristics (OR = 1.9) (Beebe-Dimmer et al., 2007). Wallner et al. (2001) in a prospective study of 2,445 Caucasian men age 40-79 years (the metabolic syndrome defined as the presence of all three metabolic components - obesity, hypertension and type 2 diabetes) found that it was minimally and inversely associated with the development of prostate cancer over 15 years of follow-up.

There may be several reasons why previous cohort studies have come to divergent conclusions regarding the metabolic syndrome and prostate cancer risk. This may be attributed to a number of factors including the size of the studies, base characteristics of those included, length of follow up, the different definitions of the metabolic syndrome used and the effects of competing factors (Hsing et al., 2007). None of the four generally accepted definitions used to define the metabolic syndrome (WHO, NCEP ATP III, EGIR and IDF) can yet be considered the gold standard, since they emphasize different aspects of the metabolic syndrome. This may in part explain differences in the results in the various studies. Furthermore, several researchers used modified versions of these accepted definitions (Lund Haheim et al., 2006; Beebe-Dimmer et al., 2009; Martin et al., 2009) or only selected parts (Beebe-Dimmer et al., 2007).

Components of Metabolic Syndrome and Prostate Cancer Risk

An adult who has a BMI of 30 kg/m^2 or higher is considered obese. According to the NHANES review, obesity amongst adult men in the Unites States of America had a prevalence of 33.3% in 2005-2006 (Ogden et al., 2007). Obesity is associated with low total testosterone and there is an inverse linear relationship between total testosterone and BMI. Free testosterone concentrations also decrease with increasing BMI. Observational studies have shown that there is an inverse relationship between serum total and free testosterone levels and visceral fat mass, and the degree of hypogonadism is positively correlated to the degree of obesity in obese men (Kapoor et al., 2005; Dandona et al., 2008).

Obesity, the principal factor in the metabolic syndrome, has been inconsistently linked to prostate cancer risk (O'Malley et al., 2006; Bianchini et al., 2002). In two large Scandinavian follow-up studies, a modest positive overall association was found (Andersson et al., 1997; Engeland et al., 2003). In the study by Andersson et al. (1997), anthropometric measurements (height and weight) and BMI were positively associated with the risk of prostate cancer, and were more strongly related to mortality than incidence. In a large prospective cohort study of 950,000 Norwegian men aged 20-74 years, stratification by age revealed that obese men age 50 to 59 years had a 58% increased prostate cancer risk compared with those with a normal BMI. The risk of prostate cancer increased by both BMI and height, and the tallest men had a relative risk (RR) of 1.72 compared with the shortest men (Engeland et al., 2003). Interestingly, Giovannucci et al. (2003) using data from the U.S. Health Professionals Follow-up Study found a significant inverse association between BMI and prostate cancer risk among men aged less than 60 years, but a weak positive association among men over 60 years (Giovannucci et al., 2003).

A prospective trial from Finland in which 1,880 patients without history of cancer or diabetes mellitus at baseline were followed for 13 years demonstrated in a multivariate analysis that, those with metabolic syndrome (WHO criteria) and a BMI ≥ 27 kg/m^2 had a three times greater risk of developing prostate cancer (Laukkanen et al., 2004). Severson et al. (1988) observed a positive association between BMI and the incidence of prostate cancer in a cohort of 8,006 Japanese men, and suggested that the lower body mass rather than the body fat played

a part in the development of prostate cancer.

Some studies suggest that components of metabolic syndrome may also result in more aggressive prostate cancer. One of these is a systematic review and meta-analysis of BMI and prostate cancer of 56 trials with 68,753 cases of prostate cancer that were identified among 2,818,767 men in 31 cohort studies, along with 13,232 cases and 16,317 controls from 25 case-control studies. There was an overall 5% increased prostate cancer risk per 5 kg/m^2 increase in BMI (MacInnis et al., 2006). For studies that reported results by stage of disease, the association with BMI was greater for the risk of advanced disease (RR 1.12 per 5 kg/m^2 increase) than for the risk of localized disease (RR 0.96 per 5 kg/m^2 increase) (MacInnis et al., 2006). Height was also positively associated with risk (RR 1.05 per 10 cm increase), but the evidence was weak for weight (RR 1.01 per 10 kg increase) (MacInnis et al., 2006).

A positive association of general adiposity with advanced prostate cancer was reported by three large cohort studies. These are the Cancer Prevention Study I (Rodriguez et al., 2001), Cancer Prevention Study II (Calle et al., 2003), and the European Prospective Investigation into Cancer and Nutrition (EPIC) (Pischon et al., 2008). In the EPIC study of 129,502 men without cancer at baseline from eight countries, during a mean follow-up of 8.5 years, 2,446 men developed prostate cancer. Body mass index, waist circumference and waist-hip ratio (WHR) were positively related to risk of total, advanced, and high-grade prostate cancer among men with lower but not among those with higher BMI (Pischon et al., 2008). A retrospective study of 1415 men showed that Caucasians with a BMI ≥ 35 kg/m^2 were approximately two to three times more likely to have worse pathologic findings during radical prostatectomy (including Gleason sum ≥ 7, positive surgical margins, extraprostatic extension, and seminal vesicle invasion) than men with BMI less than 25 kg/m^2 (Jayachandran et al., 2009). Obesity was associated with a greater risk of recurrence among overweight or obese Caucasian and African-American men (Jayachandran et al., 2009). An earlier prospective study further demonstrated that significantly higher fasting plasma insulin levels were observed in men who died compared with those who survived prostate cancer. Furthermore, prostate cancer mortality was significantly associated with a number of metabolic features present (Jayachandran et al., 2005).

A prospective study of 320 patients in whom clinical prostate cancer, stages T2-3 further demonstrated that the men who died of clinical prostate cancer during the follow-up period were had a significantly higher stage and grade of clinical prostate cancer at baseline than men still alive with clinical prostate cancer at follow-up. Prostate cancer mortality was significantly associated with lower HDL-cholesterol level and a higher WHR (Hammarsten and Högstedt, 2005). Another prospective study by the same authors involving 299 Swedish men with clinical prostate cancer demonstrated that both prostate cancer stage and grade are directly associated with BMI, triglyceride, waist measurement, and fasting plasma insulin, and indirectly with HDL-cholesterol (Hammarsten and Högstedt, 2004).

The WHR included in the WHO criteria is a trustworthy indirect parameter for measuring central obesity, which is fundamental for determining metabolic syndrome physiopathology (World Health Organization, 1999). In the systematic review and meta-anal¬ysis of BMI and prostate cancer in 56 trials by MacInnis et al. (2006), the WHR had a relative risk for prostate cancer of 1.11 per 0.1 unit increase. These results support the proposed hypothesis that visceral fat has a role in metabolic syndrome physiopathology and has a direct influence promoting prostate cancer. The case-control study of Chinese men (128 case and 306 control subjects) performed by Hsing et al. (2003) showed that a high WHR, but not the BMI, was positively associated with prostate cancer risk, was extended to include serum fasting insulin concentration.

In univariate analysis, positive associations with prostate cancer prevalence and hyperglycemia low HDL-cholesterol, as well as elevated WHR, SBP, and DBP have also been observed (de Santana et al., 2008; Coman et al., 2008). A prospective cohort based on 29,364 Norwegian men followed up for prostate cancer incidence and mortality from 1995-1997 to the end of 2005 in the second Nord Trøndelag Health Study (HUNT 2) showed little evidence that baseline BMI, waist circumference, WHR, total or HDL-cholesterol, or triglycerides were associated with incident or fatal prostate cancer. However, there was weak evidence that each 12-mm increase in DBP was independently associated with an 8% increase risk of incident prostate (Martin et al., 2009). Data from the Helsinki Heart Study of a cohort of 18,939 Finnish middle-aged men showed that patients with BMI greater than 28 kg/m^2 and SBP greater than 150 mmHg were greater than two times more likely to have prostate cancer, and greater than three times more likely with the addition of low HDL-cholesterol (≤ 1.05 mmol/L) (Tuohimaa et al., 2007). Investigators have also reported positive associations among WHR, DBP, and serum PSA in those with prostate cancer, as well as an inverse relationship between HDL-cholesterol and serum PSA (Han et al., 2008).

Hypogonadism, Metabolic Syndrome and Prostate Cancer

Androgen deficiency in males is considered a syndrome that is characterized by the presence of defined signs/symptoms in conjunction with low testosterone levels (The Endocrine Society, 2001. Epidemiological studies (Morley et al., 1997; Araujo et al., 2004) and a survey of clinical practice (Mulligan et al., 2006) have shown that the prevalence of male hypogonadism is higher than previously thought. One epidemiological study found a prevalence of 6.0-12.3% in men in the United States of America aged 40-69 years (Araujo et al., 2004). Data from Physicians' Clinical Practice (including men aged 45 years or older) suggest a prevalence of 38.7% in men aged ≥45 years (Mulligan et al., 2006).

Male hypogonadism has surfaced as an independent risk factor for metabolic syndrome. A link between the metabolic syndrome and hypogonadism has been suggested (Guay et al., 2009) and it has been shown that

nearly all aspects of the metabolic syndrome are associated with reduced testosterone levels (Phillips et al., 2003; Svartberg et al., 2004; Stellato et al., 2000). A cross-sectional study showed that men with low testosterone levels have a higher prevalence of metabolic syndrome (Muller et al, 2005). A population-based prospective cohort of 1,004 adults aged 20-79 years with metabolic syndrome defined by NCEP ATP III guidelines showed that low testosterone predicts development of incident metabolic syndrome especially in young men aged 20-39 years (Laaksonen et al., 2004).

There are several hypotheses concerning the mechanism linking the metabolic syndrome and male hypogonadism. Obesity, especially visceral obesity, is an established aspect of the metabolic syndrome. Activity of aromatase, an adipose enzyme that is involved in the irreversible conversion of testosterone into estradiol (Cohen, 2008) is higher in men who are obese and, consequently, they tend to have decreased testosterone level and increased estradiol level (Cohen, 2008; Cohen et al., 1993). The link between the metabolic syndrome and hypogonadism can also be explained by the mechanism of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis has been shown to be overactive in sub¬jects suffering from the metabolic syndrome (Rosmond et al., 1998) and it is well established that cortisol inhibits the reproductive axis at several levels including secretion of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) and also at the level of the testes themselves (Chrousos, 1998). This emerging link between male hypogonadism and the metabolic syndrome via hypogonadotropic hypogonadism, increased aromatase activity, and increased activity of the HPA axis seems to suggest that male hypogonadism is also a urological aspect of the metabolic syndrome.

Sex steroid hormones are thought to contribute to the growth, differentiation, and progression of prostate cancer. Low testosterone, a condition associated with metabolic syndrome, has also been linked to more severe prostate cancer. In the retrospective case-control Health Professionals Follow-up Study of 460 prostate cancer men, those with low total plasma testosterone (< 3 ng/mL) had an elevated risk of high-grade prostate cancer (Gleason sum ≥ 7; OR = 2.59) (Platz et al., 2005). Lower testosterone levels have also been significantly correlated with adverse pathological stage on multivariate analysis, as did clinical stage, biopsy grade and PSA (Isom-Batz et al., 2005). In addition, low total testosterone is more frequently present with positive surgical margins in radical retropubic prostatectomy (Teloken et al., 2005). Yet other investigators have failed to find relationships between testosterone levels and risk of prostate cancer or more aggressive forms (Morote et al., 2009). Morote et al (2009) analyze the relationship between the levels of total and free serum testosterone and the risk of prostate cancer and tumour aggressiveness in 478 patients. The cancer detection rate in hypogonadal patients was 41.3% (33/80) and 46.0% in eugonadal patients (183/398). The median level of total testosterone was 433 ng/dL in patients with low-risk prostate cancer, 467 ng/dL in those with intermediate-risk tumours and 468 ng/dL in those with high-risk tumours. The median levels of free testosterone were 9.4, 9.8 and 10.3 pg/mL, respectively. The authors suggest that prostate cancer risk and tumour aggressiveness are not related to serum levels of total and free testosterone (Morote et al., 2009).

Androgen Deprivation Therapy, Metabolic Syndrome and Prostate Cancer

Androgen deprivation therapy is the most widely used therapeutic modality in prostate cancer (Loblaw et al., 2007). Androgen suppression can be achieved by means of orchiectomy or the use of GnRH agonists. About one-third of the estimated two million prostate cancer survivors in the United States of America currently receive treatment with a GnRH agonist (Smith, 2007). In some cases, androgen receptor antagonists are used in conjunction with GnRH analogues to block the action of adrenal androgens (Basaria, 2008).

Androgen deprivation therapy has since become the main treatment for metastatic or recurrent prostate cancer. In metastatic disease, ADT has been shown to improve cancer-related morbidities such as quality of life and bone pain (Chodak et al., 2002). The use of ADT is increasing with the advocacy of adjuvant ADT in otherwise asymptomatic patients with locally advanced prostate cancer, and the inclusion of adjuvant temporary ADT in the multi-modal treatment of high risk localized prostate cancer (Hakimian et al., 2008). When initiated for systemic disease or as monotherapy for clinically localized disease, ADT is typically continued life-long, and many men live with the side effects of ADT for many years (Pound et al., 1999). While older men with prostate cancer have a higher incidence of low-risk disease characteristics, they are more likely to be treated with ADT than other modalities including watchful waiting (Mohile 2003). The CaPSURE study, an observational database of 7,195 patients with prostate cancer shows that the use of primary ADT increased dramatically between 1989 and 2001, from 4.6% to 14.2% in low-risk, 8.9% to 19.7% in immediate-risk, and from 32.8% to 48.2% in high-risk patients. The use of neoadjuvant ADT also increased in association with radical prostatectomy (2.9% to 7.8%) and external beam radiation therapy (9.8% to 74.6%) across all risk levels combined (Cooperberg et al., 2004). Rates of neoadjuvant ADT use among patients treated with brachytherapy also increased but not statistically significantly (7.4% to 24.6%) (Cooperberg et al., 2004).

Data suggest that immediate adjuvant use of ADT after radical prostatectomy and pelvic lymphadenectomy improves survival and reduces the risk of recurrence in patients with node-positive prostate cancer (Messing et al., 1999). Androgen deprivation therapy has been shown to be effective for palliation in many patients with advanced prostate cancer and improves outcomes for high-risk patients treated with radiation therapy for localized disease (Sharifi et al., 2005; Bolla et al., 1997). Local surgery and/or radiation therapy are the preferred treatment modalities in men with locally confined prostate cancer. However, ADT is now being used even in men with early-stage prostate cancer and in men who experience biochemical

recurrence (Chodak, 1998). This is achieved either with bilateral orchiectomy or with GnRH agonists.

The intentional consequence of treatment with a GnRH agonist is hypogonadism. Gonadotropin-releasing hormone agonists decrease serum concentrations of testosterone by over 95% and estrogen by approximately 80% (Garnick, 1986). They have a variety of adverse effects related to gonadal steroid deficiency, including decreased libido, decreased lean body mass (LBM), increase in BMI and muscle strength, increased fat mass, impotence, decreased quality of life, osteopenia with increased fracture risk, changes in cognition and mood, and vasomotor flushing (Basaria and Dobs, 2001; Sharifi et al., 2005). The increase in fat mass is secondary to the deposition of both subcutaneous and visceral fat, resulting in abdominal obesity (Basaria et al., 2002; Muller et al., 2005). The increase in visceral fat results in elevated levels of adipokines, which, in turn, are responsible for causing insulin resistance (Eckel et al., 2005). A prospective study of 40 men with locally advanced, node-positive or biochemically recurrent prostate cancer who had ADT showed an increase in average weight (2.4 ± 0.8%), percentage fat body mass (9.4 ± 1.7%) and a decrease in percentage LBM (2.7 ± 0.5%) (Smith et al., 2002). While there was an increase in cross-sectional areas of the abdomen (3.9 ± 1.2%), and abdominal subcutaneous fat (11.1 ± 3.4%), the cross-sectional area of intra-abdominal fat did not change significantly (Smith et al., 2002).

Less well-known adverse effects of ADT are dyslipidaemia, increased peripheral insulin resistance, and the development of metabolic syndrome that might contribute to an increased risk of type 2 diabetes mellitus and cardiovascular disease (Stellato et al., 2000). In a cross-sectional study of 53 men with prostate cancer on long-term ADT, those on ADT have significantly elevated levels of fasting insulin and glucose compared with eugonadal men with prostate cancer (not on ADT) and age-matched controls (Basaria et al., 2006). This significance was maintained even after adjustment for age and BMI. Therefore these men are at risk for developing insulin resistance and hyperglycemia, thus leading to increased risk of cardiovascular disease (Basaria et al., 2006). Furthermore, in a 12-week prospective study of 25 non-diabetic men with locally advanced or recurrent prostate cancer on short-term GnRH agonist treatment, the mean insulin sensitivity by HOMA-IR decreased by 12.9% from baseline. The fat body mass significantly increased by 4.3% and fasting plasma insulin levels increased by 25.9% (Smith and Nathan, 2006). Another short-term prospective study of 22 men with prostate cancer undergoing ADT showed a significant increase in fasting insulin levels after three months (median serum insulin rose from 11.8 to 15.1 mU/liter at one month, and to 19.3 mU/liter after three months) of treatment. However, there was no significant change in plasma glucose levels (Smith et al., 2001).

Gonadotropin-releasing hormone agonists alter serum lipoproteins in men with prostate cancer. In a study of 26 elderly men receiving treatment with leuprolide, a luteinizing hormone-releasing hormone agonist, mean total cholesterol levels significantly increased by 10.6%, HDL-cholesterol increased by 8.2% and triglycerides increased by 26.9%; LDL-cholesterol levels were unchanged (Eri et al., 1995). In another prospective study of 40 men with non-metastatic prostate cancer treated with leuprolide for 48 weeks, the serum total cholesterol, HDL-cholesterol, and LDL-cholesterol increased significantly by 9.0, 11.3, and 7.3%, respectively, after 12 months. Serum triglycerides increased significantly by 26.5% (Smith et al., 2002).

In a cross-sectional study comparing 16 men undergoing ADT for at least 12 months, 14 age-matched eugonadal men with non-metastatic prostate cancer who had local therapy, and 14 age-controlled eugonadal men with no previous history of diabetes mellitus or dyslipidaemia, men on ADT had a higher BMI than the other groups. Men in the ADT group had significantly higher levels of total cholesterol compared to the other two groups (Braga-Basaria et al., 2006a). In a prospective clinical trial of 1,102 men comparing medical castration between abarelix and leuprolide acetate, vs leuprolide acetate and antiandrogen bicalutamide, fasting serum lipid, glucose levels and HbA1c were determined at baseline and on treatment days 85 and 169 (Yannucc et al., 2006). There were significant increases in total cholesterol, triglyceride and HDL-cholesterol in patients on leuprolide acetate or abarelix, but not in patients on leuprolide acetate plus bicalutamide. No consistent changes in LDL-cholesterol were detected. Hemoglobin A1c increased from baseline to day 85 only and there were no changes in fasting glucose measurements (Yannucc et al., 2006).

In a cross-sectional study comparing 20 men with prostate cancer undergoing ADT for at least 12 months, 18 age-matched men who received local treatment for localized prostate cancer and 20 aged-matched controls, the prevalence of metabolic syndrome (defined according to NECP ATP III) was higher in the ADT than in the non-ADT and control groups. Among the components of metabolic syndrome, men on ADT had a higher prevalence of abdominal obesity and hyperglycemia. Androgen-deprived men also had significantly elevated triglycerides compared with controls (Braga-Basaria et al., 2006b). Among the components of metabolic syndrome, men on ADT had a higher prevalence of abdominal obesity, hyperglycaemia and elevated triglyceride than the controls.

In a prospective study, 49 patients with non-metastatic prostate cancer had total androgen blockade with a combination of luteinizing hormone releasing hormone (LHRH) agonist or bilateral orchidectomy (seven), with oral flutamide as a neoadjuvant therapy for six months before radical therapy (Nishiyama et al., 2005). Compared to their baseline levels, the mean body weight, fasting blood glucose and total cholesterol levels all increased significantly (Nishiyama et al., 2005). Consistent with these results, a large population-based study of a cohort of 73,196 men diagnosed with locoregional prostate cancer demonstrated that GnRH agonists are associated with a greater risk of incident diabetes mellitus but not coronary heart disease, myocardial infarction, or sudden cardiac death (Keating et al., 2006).

Vitamin D, Prostate Cancer and Metabolic Syndrome

The NHANES data demonstrated that Vitamin D insufficiency is a common public health problem nationwide, especially for elderly and minority populations (Zadshir et al., 2005). A role for Vitamin D in decreasing prostate cancer risk has been hypothesized on the basis of observations of older age, higher prostate cancer incidence in men of African descent, higher prostate cancer mortality in regions of low solar radiation exposure, northern latitudes, all of which are associated with lower Vitamin D status (Schwartz and Hulka, 1990; Hanchette and Schwartz, 1992; Schwartz, 2005).

Epidemiological data from prospective studies showed inconsistent associations of pre-diagnostic circulating levels of Vitamin D metabolites, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D with prostate cancer incidence. Corder et al. (1993) evaluated the risk of prostate cancer in relation to serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. They reported an inverse association for circulating 1,25-dihydroxyvitamin D and aggressive prostate cancer, particularly in older men or in those with low 25-hydroxyvitamin D. In men greater than equal to 57 years of age, 1,25-dihydroxyvitamin D was an important predictor of risk for palpable and anaplastic tumors (Corder et al., 1993).

Two studies of European Nordic countries measured only the 25-hydroxyvitamin D metabolite. The first was a nested case-control study based on a 13-year follow-up of about 19,000 middle-aged men within the Helsinki Heart Study who were free of clinically verified prostate cancer at baseline (Ahonen et al., 2000). The authors reported low levels of 25-hydroxyvitamin D associated with an increased risk for subsequent earlier exposure and more aggressive development of prostate cancer, especially before the andropause. The prostate cancer risk was highest among younger men (< 52 years) at entry and low serum 25-hydroxyvitamin D (OR 3.5 adjusted) (Ahonen et al., 2000). The second was a longitudinal nested case-control study on Nordic men using serum banks of 200,000 samples found that both low and high 25-hydroxyvitamin D levels were associated with an increased risk (Tuohimaa et al., 2004). Li et al. (2007) in a study involving 18 years of follow-up of 14,916 men initially free of diagnosed cancer reported an the inverse association of 1,25-hydroxyvitamin D alone or together with 25-hydroxyvitamin D with aggressive prostate cancer which provide further evidence that both 25-hydroxyvitamin D and 1,25-hydroxyvitamin D may play an important role in preventing prostate cancer progression, especially among older men.

Factors related to the metabolic syndrome and low levels of Vitamin D have been implicated as risk factors for prostate cancer. Tuohimaa et al. (2007) investigated the associations of Vitamin D with the metabolic syndrome factors, and the prostate cancer risk associated with these factors in a longitudinal nested case-control study on 132 prostate cancer cases and 456 matched controls from a cohort of 18,939 Finnish middle-aged men from the Helsinki Heart Study. They found that a clustering of factors related to the metabolic syndrome substantially increased the prostate cancer risk but only if the level of Vitamin D was low. Univariate analysis showed that men in the highest quartiles of body mass index (>28 kg/m^2) and systolic blood pressure (>150 mmHg) showed a modest increase in risks of prostate cancer with ORs of 1.37 and 1.53 respectively. However when these two factor along with low HDL-cholesterol were present jointly with low Vitamin D (< 40 nmol/L), the OR was 8.03 compared with those with no metabolic syndrome factors and intermediate levels (Tuohimaa et al., 2007).

The existence of a common putative pathway(s) may provide an explanation for the interaction of Vitamin D and metabolic syndrome factors on prostate cancer risk. Possible factors explaining this interaction include those among endocrine systems that are affected both by inadequate Vitamin D status and metabolic syndrome and play a central role in the regulation of prostatic growth. The peroxisome proliferator-activated receptors are nuclear receptors that bind to fatty-acid-derived ligands and activate the transcription of genes that govern lipid metabolism. They play important regulatory roles in the metabolic syndrome, including insulin sensitivity, inflammation, adipogenesis and lipid metabolism. Endogenous ligands of peroxisome proliferator-activated receptor-γ include oxidized lipids and fatty acids (Shulman and Mangelsdorf, 2005). These receptors bind to the retinoid X receptor to form a heterodimer. Circulating 25-hydroxyvitamin D is converted to the active hormone 1,25-dihydroxyvitamin D which operating through the Vitamin D receptor. The Vitamin D receptor forms a heterodimer with retinoid X receptor, and these two complexes have common signaling pathway, thus influencing tightly each other's effect on the target gene (Shulman and Mangelsdorf, 2005). Both these receptors are highly expressed in prostate cancer cells where they are involved in regulation of growth and induction of apoptosis (Peehl and Feldman, 2003).

Another possible pathway is the involvement of Vitamin D in the insulin-like growth factor (IGF) signaling axis (Stewart and Weigel, 2004), a mechanism which may be involved in the action of factors of metabolic syndrome (Attia et al., 1998). Insulin-like growth factor-I may stimulate the development of prostate cancer by stimulating cell proliferation and by inhibiting apoptosis (Jones and Clemmons, 1995; Dunn et al., 1997). *In vitro* studies have demonstrated that prostatic epithelial cells respond to the mitogenic activity of IGF-I (Cohen et al., 1991; Iwamura et al., 1993). The up-regulation of IGF-binding protein-3 by Vitamin D may be one mechanism mediating the anti-proliferative effect of this hormone on prostatic epithelial cells (Boyle et al., 2001; Sprenger et al., 2001). Insufficient Vitamin D with prevalent hyperinsulinemia could contribute to prostate carcinogenesis, permitting unbalanced mitotic effect of free IGF-I on prostatic cells (Tuohimaa et al., 2007).

Conclusion and Future Directions

Metabolic syndrome and prostate cancer remain two growing health problems affecting millions of men and the information presented in this review indicates that there is an association between prostate cancer and metabolic syndrome. However there are studies that do not uniformly suggest that metabolic syndrome is important.

The classic metabolic syndrome is characterized by visceral obesity, insulin resistance, low HDL-cholesterol, high triglycerides, elevated C-reactive protein, and low adiponectin levels. Insulin resistance and hyperinsulinemia are the cornerstone of metabolic syndrome and are also factors for prostate cancer. Among the physio-pathological entities that comprise metabolic syndrome, the serum level IGF-I seems to be the one that is most closely linked with prostate cancer. Other common potential denominators linking the metabolic syndrome and prostate cancer could be alterations in, insulin-like growth factor binding proteins, and total and bioavailable plasma sex hormone levels, including testosterone and sex hormone binding globulin levels To dissect these interrelated factors, future prospective studies should be sufficiently large, with better assessment of the metabolic factors in order to clarify the complex interplays of these factors on prostate cancer risk. This may have important clinical implications for future directions in prostate cancer research and ultimately its prevention and treatment.

Androgen deprivation therapy is the most widely used therapeutic modality in prostate cancer. Androgen suppression can be achieved by means of orchiectomy or the use of GnRH agonists. The intentional consequence of treatment with a GnRH agonist is hypogonadism. Male hypogonadism has emerged as an independent risk factor in the development of metabolic syndrome. There are several hypotheses concerning the mechanism linking the metabolic syndrome and male hypogonadism. Gonadotropin-releasing hormone agonist treatment for men with locoregional prostate cancer may be associated with an increased risk of incident diabetes mellitus and CVD. The benefits of GnRH agonist treatment should be weighed against these potential risks. Additional research is needed to identify populations of men at highest risk of treatment-related complications and to develop strategies to prevent treatment-related diabetes and CVD. There is also data that demonstrates that men undergoing long-term ADT have higher total and LDL-cholesterol than age-matched controls. Long-term prospective studies are needed to determine the time of onset of changes in these lipoproteins while on ADT and the influence of these changes on cardiovascular mortality.

Vitamin D inhibits the development and growth of prostate cancer cells. Epidemiologic results on serum vitamin D levels and prostate cancer risk have, however, been inconsistent. Factors related to the metabolic syndrome and low levels of vitamin D have been implicated as risk factors for prostate cancer. The existence of a common putative pathway(s) may provide an explanation for the interaction of vitamin D and metabolic syndrome factors on prostate cancer risk.

Acknowledgement

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