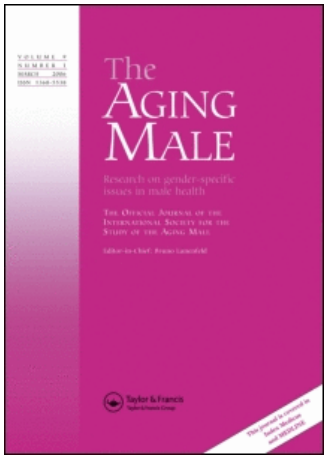

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Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes

Ahmad Haidar; Aksam Yassin [a]; Farid Saad [bc]; Ridwan Shabsigh [de]
[a] Department of Urology, Gulf Medical College School of Medicine, Ajman
[b] Research Department, Gulf Medical College School of Medicine, Ajman
[c] Bayer Schering Pharma, Berlin, Germany
[d] Division of Urology, Maimonides Medical Center, Brooklyn, USA
[e] Columbia University, New York, USA

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Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes

AHMAD HAIDAR[1], AKSAM YASSIN[2,3], FARID SAAD[4,5], & RIDWAN SHABSIGH[6,7]

[1]*Urologic Office, Bremerhaven, Germany,* [2]*Segeberger Kliniken, Hamburg-Norderstedt, Germany,* [3]*Department of Urology, Gulf Medical College School of Medicine, Ajman, UAE,* [4]*Research Department, Gulf Medical College School of Medicine, Ajman, UAE,* [5]*Bayer Schering Pharma, Berlin,Germany,* [6]*Division of Urology, Maimonides Medical Center, Brooklyn, USA, and* [7]*Columbia University, New York, USA*

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Abstract

Introduction and objective. Androgen deprivation therapy of prostate cancer with luteinizing hormone releasing hormone agonists may result in loss of bone mass, changes in body composition and a deterioration of arterial stiffness. The present study monitored the effects of androgen deprivation therapy in men with insulin-dependent diabetes on glycaemic control and on biochemical cardiovascular risk markers.

Methods. Twenty-nine patients from a urology practice were included. All men had insulin-dependent diabetes mellitus prior to being diagnosed with metastatic prostate cancer. In a retrospective analysis, levels of fasting glucose, haemoglobin A1c, insulin requirements, total cholesterol, HDL, LDL, triglycerides, fibrinogen, PAI-1, tPA and C-reactive protein were obtained on at least eight occasions over a period of up to 24 months.

Results. Glycaemic control worsened substantially with increases of serum glucose requiring increases in insulin dosages. HbA1c levels rose indicating impaired glycaemic control. All biochemical cardiovascular risk markers deteriorated.

Conclusion. In men with insulin-dependent diabetes, androgen deprivation therapy may have negative effects on their glycaemic control and may aggravate the biochemical risk profile of cardiovascular disease to which diabetics are predisposed. These observations are in agreement with the emerging role of low levels of testosterone in metabolic syndrome and insulin resistance.

Keywords: *Diabetes, androgen deprivation therapy, prostate cancer, hypogonadism, testosterone*

Introduction

Androgen deprivation therapy remains the treatment of first choice for metastatic adenocarcinoma of the prostate [1,2]. The commonly known adverse effects of androgen deprivation therapy include decreased libido, erectile dysfunction, hot flushes, loss of bone mineral density and changes in body composition [3–6]. Less known adverse effects are the metabolic alterations in the insulin-glucose regulating system and in the cardiovascular system. Since prior literature suggested that androgen deficiency increased peripheral insulin resistance, the need arose to investigate the metabolic effect of androgen deprivation therapy in prostate cancer patients with diabetes. The understanding of such metabolic effects of androgen deprivation therapy will help urologists as well as endocrinologists, diabetologists and primary care practitioners manage patients newly initiated into androgen deprivation therapy. The goal of this study was to explore the effects of the initiation of androgen deprivation on the glycaemic control and on cardiovascular biochemical risk markers in patients with insulin-dependent diabetes mellitus.

Subjects and methods

Patient population. Twenty-nine patients in a single urology practice were included in this retrospective review of their charts and laboratory values. All men had insulin-dependent diabetes type II before being diagnosed with metastatic prostate cancer. At the time of the initiation of androgen deprivation therapy, the age range was 58 to 84 years and the mean age was 75 years. The baseline data of these patients are shown in Table I. All patients received standard doses of luteinizing hormone releasing hormone (LHRH) agonist therapy.

Outcome measurements. Outcome measurements were obtained on 5 to 8 occasions over a period of up to 24 months, depending on patient survival. Glycaemic control was assessed by measuring the levels of

Correspondence: Ridwan Shabsigh MD, Division of Urology, Maimonides Medical Center, Brooklyn, NY 11214, USA. Tel: +1 718 283 7746. Fax: +1 718 635 7424. E-mail: rshabsigh@maimonidesmed.org

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Table I. Baseline data.

Demographics, co-morbidities and testosterone	$n = 29$
Mean age (58–85yr)	74 yr
Age range	58–85 yr
Total serum testosterone	
≤6.9 nmol/L	15 patients
7.0–11.7 nmol/L	7 patients
12.1 and 13.0 nmol/L	2 patients
Unknown	5 patients
Smokers	13 patients
Co-morbidities	
Diabetes mellitus Type II	29 patients
Hypertension	22 patients
Dyslipidemia	14 patients
Hyperuricemia	12 patients
Cardiovascular diseases	16 patients

fasting glucose, haemoglobin A1c (Hgb A1c) and recording the insulin dose requirements. Cardiovascular risk was assessed by measuring the cardiovascular biochemical risk markers, C-reactive protein (CRP), fibrinogen, plasminogen activator-1 (PAI-1), tissue plasminogen activator (tPA) and the lipid profile including total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and triglycerides.

Statistical analysis. The data of this retrospective analysis were not normally distributed and time periods between two consecutive measurements in subjects were not identical, with variations of 2–3 weeks difference between them. The samples were relatively small. Therefore, median and range of values were used to describe the results. The non-parametric Friedman test was used for testing the time course of the variables measured. For all statistical testing, the differences were considered significant if p value $\leq .05$.

Results

Glycaemic control. During the period of observation, measurements of glycaemic control worsened substantially in all 29 men. Fasting serum glucose increased from 143.2 ± 26.823 mg/dL at baseline prior to androgen deprivation therapy up to 187.3 ± 30.229 mg/dL at end of observation following androgen deprivation therapy (Figure 1A). Hgb A1c levels increased from $6.3 \pm 1.045\%$ at baseline prior to androgen deprivation therapy up to $9.3 \pm 1.198\%$ at end of observation following androgen deprivation therapy (Figure 1B). These increases suggested progressively impaired glycaemic control.

Insulin requirements. There were remarkable increases in the daily doses of insulin required to treat the diabetes from 26.1 ± 7.219 units at baseline up to 48.2 ± 9.948 units at the end of the observation following androgen deprivation (Figure 1C).

Cardiovascular biochemical risk markers. All cardiovascular biochemical risk markers deteriorated: CRP from 1.3 ± 0.504 to 2.3 ± 0.556 mg/dL (Figure 2A), fibrinogen ($n = 13$) from 3.0 ± 1.134 to 13.0 ± 0.583 g/L (Figure 2B), PAI-1 ($n = 6$) from 36.9 ± 7.590 to 69.0 ± 13.957 μ/L (Figure 2C), and t-PA ($n = 6$) from 124.9 ± 36.245 to 185.7 ± 22.322 (Figure 2D). Similarly the lipid profile deteriorated with total cholesterol from 252.0 ± 41.143 to 322.3 ± 41.097 mg/dL (Figure 3A), HDL-C from 31.4 ± 6.349 to 20.9 ± 2.226 mg/dL (Figure 3B), LDL-C from 184.5 ± 16.311 to 229.1 ± 21.006 mg/dL (Figure 3C), and triglycerides from 207.4 ± 39.301 to 283.9 ± 49.679 mg/dL (Figure 3D).

Cause of death. The cause of death was known in 24 patients (Table II). Cardiovascular causes of death occurred in 10 patients (34%), including cerebrovascular accident, myocardial infarction and cardiopulmonary failure. The cause of death was attributable to metastatic prostate cancer in 9 patients (31%). In 5 patients, the cause of death was unknown.

Discussion

In this study, androgen deprivation led to a profound deterioration of the glycaemic control in prostate cancer patients with insulin-dependent diabetes mellitus. This deterioration was evident based on multiple observations. The first observation was the significant increase in fasting glucose and HgbA1c. A steady rise in fasting glucose and Hgb A1c was observed in a linear fashion. Haemoglobin A1c increased from a reasonably adequate control of diabetes to a poorly controlled diabetes (Figure 1B). The second observation was the increase in insulin doses required for diabetes control. Of great concern was the observation that diabetes control worsened in spite of the increased insulin doses. This attests to the profound effect of androgen deprivation on peripheral insulin resistance.

All biochemical risk markers of cardiovascular disease deteriorated. Our observation is in agreement with a case report on two patients receiving androgen deprivation therapy for prostate cancer [7]. One case was a man with diabetes mellitus type II showing a similar deterioration of glycaemic control, the other developed diabetes mellitus upon initiation of androgen deprivation therapy. The glycaemic control of the two patients in the this case report [7] improved considerably upon treatment with pioglitazone, a peroxisome-proliferator-activated receptor gamma agonist which is a powerful insulin sensitizer, not only improving glycaemic control but also improving other features of insulin resistance syndrome [8]. This observation indirectly substantiates the notion that androgen deprivation therapy leads to insulin resistance.

Over the last years several studies have found an inverse relationship between testosterone levels and

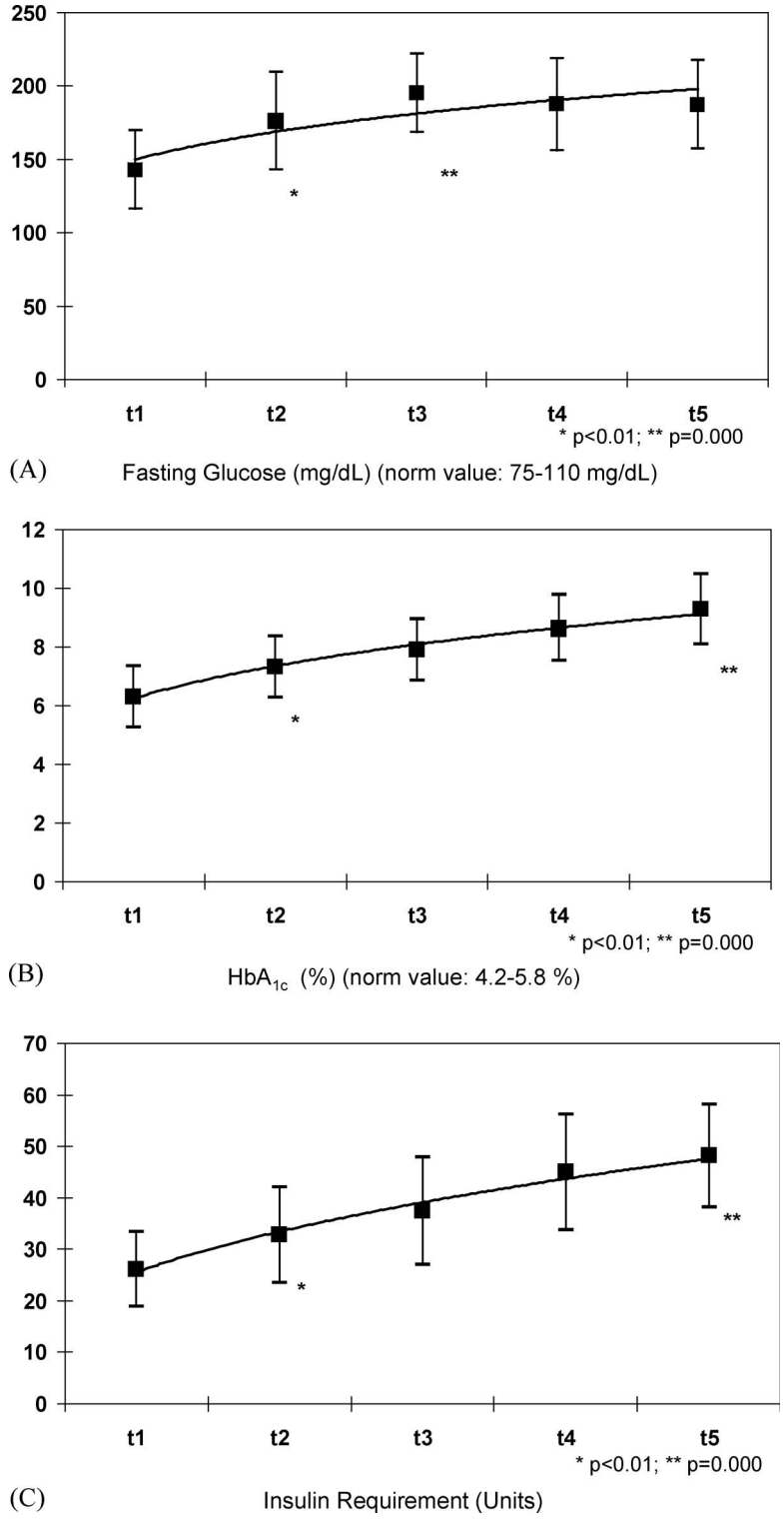
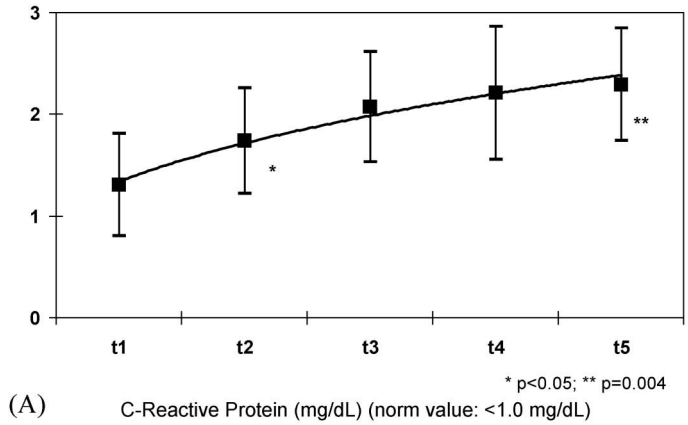
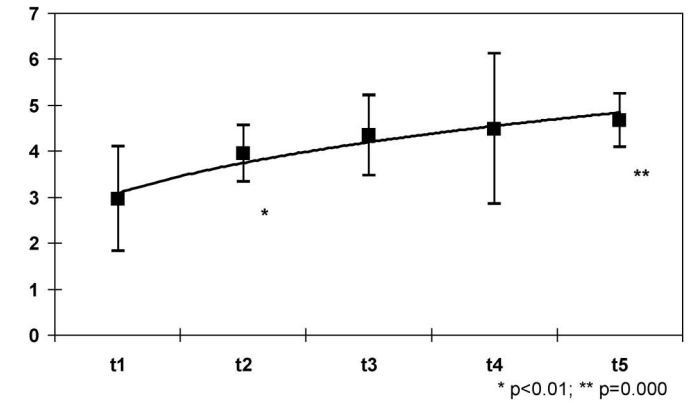


Figure 1. Worsening of glycaemic control after initiation of androgen deprivation therapy, as evidenced by (A) Increasing fasting glucose, (B) Increasing Hgb A 1c, and (C) Increasing insulin dose requirements.

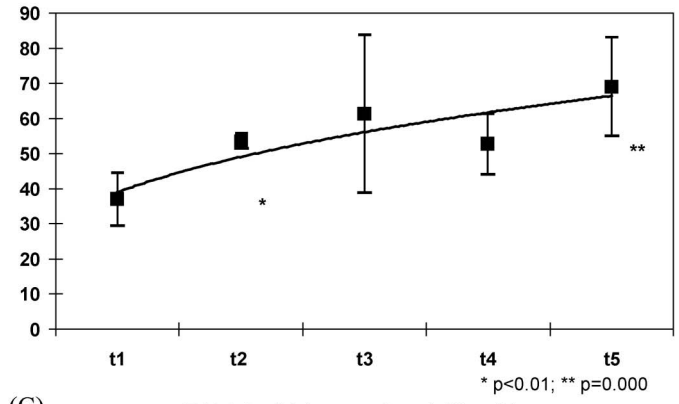
the prevalence of diabetes. Men with diabetes type II have lower testosterone levels than weight-matched non-diabetic control subjects [9–11]. In addition, six large prospective studies have shown that low testosterone levels predict development of diabetes type II in men [12–17]. Two studies demonstrated a positive relationship between total testosterone levels and insulin sensitivity in normal [18] and diabetic men [19]. In contrast, data on the relationship between free testosterone levels and insulin sensitivity are conflicting, with two studies showing no correlation [19,20], whereas a third study demonstrates a weak positive relationship [18]. However, measurement of free testosterone is fraught with methodological difficulties [21]. A recent study found an association between total and bioavailable



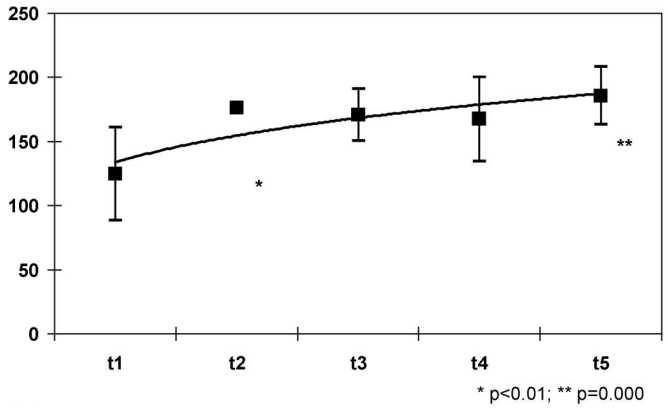
(A) C-Reactive Protein (mg/dL) (norm value: <1.0 mg/dL)



(B) Fibrinogen (g/L) (norm value: 1.7-4.0 g/L)

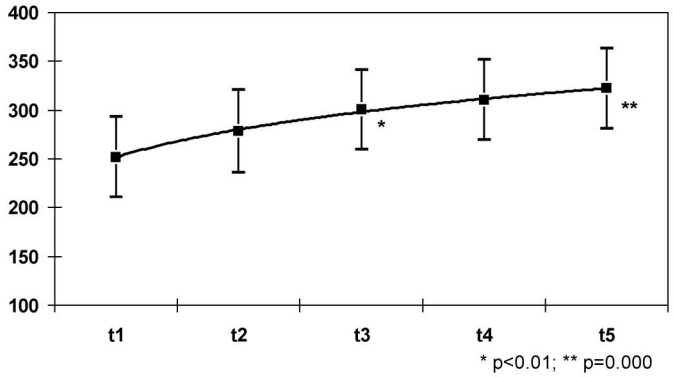


(C) PAI-1 (µg/L) (norm value: 4-43 µg/L)

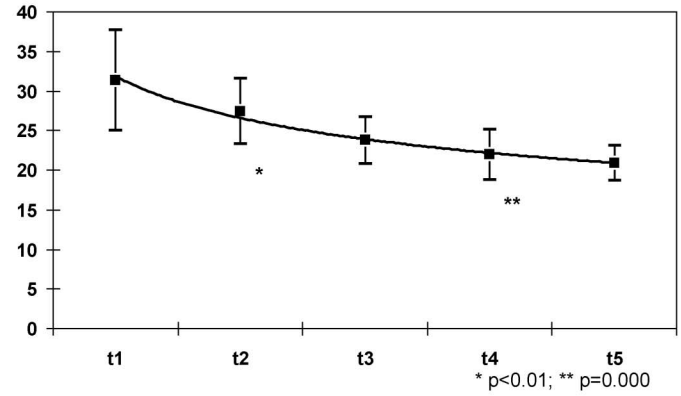


(D) t-PA (%) (norm value: 75-150 %)

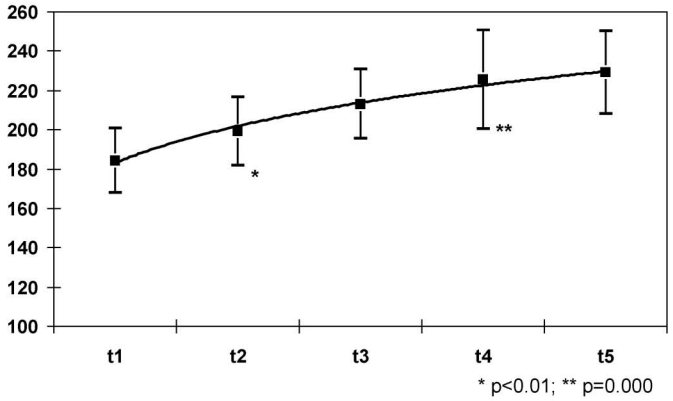
Figure 2. Deterioration of cardiovascular biochemical risk markers after initiation of androgen deprivation therapy, as evidenced by (A) increasing CRP, (B) increasing fibrinogen, (C) increasing PAI-1 and (D) increasing t-PA.



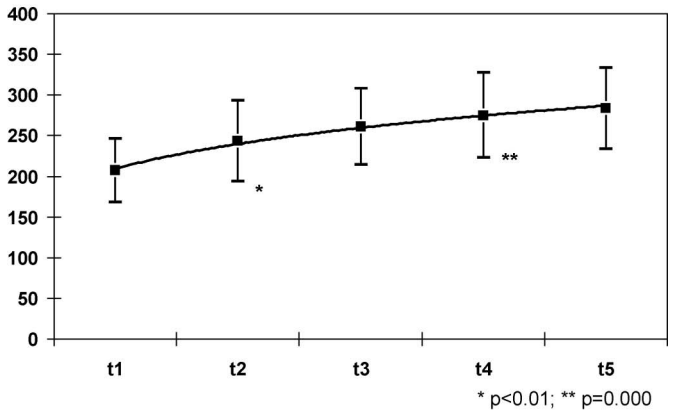
(A) Total Cholesterol (mg/dL) (norm value: < 220 mg/dL)



(B) HDL Cholesterol (mg/dL) (norm value: 35-55 mg/dL)



(C) LDL Cholesterol (mg/dL) (norm value: 150-190 mg/dL)



(D) Triglycerides (mg/dL) (norm value: < 180 mg/dL)

Figure 3. Deterioration of lipid profile after initiation of androgen deprivation therapy, as evidenced by (A) increasing total cholesterol, (B) decreasing HDL, (C) increasing LDL and (D) increasing triglycerides.

Table II. Cause of death of patients with prostate cancer and diabetes 16–28 months after initiation of androgen deprivation therapy.

Cause of death	Number of patients
Metastatic prostate cancer	9
Cardiopulmonary failure	2
Cerebrovascular accident	5
Pneumonia	4
Myocardial infarction	3
Sepsis	1
Unknown	5
Total	29

testosterone and features of the metabolic syndrome [22].

The prevalence of prostate cancer increases significantly with aging. It is of note that aging itself is also accompanied by insulin resistance and a decline in testosterone levels [22–29]. A recent study demonstrated a positive correlation between serum testosterone levels and insulin sensitivity in men across the full spectrum of glucose tolerance [30]. In this study, men with hypogonadal testosterone levels were twice as insulin resistant as their eugonadal counterparts, and 90% fulfilled criteria for metabolic syndrome. One of the characteristics of metabolic syndrome is insulin resistance. Insulin resistance has assumed increasing importance as a risk factor for cardiovascular disease. Recent studies using genetic analysis [31,32], or functional imaging [33,34], have shed light on the role of mitochondrial function in inducing metabolic disturbances characteristic of insulin resistance. The study of Pitteloud et al. [30] demonstrated that testosterone levels correlate not only with insulin sensitivity but also with genetic (OXPHOS gene expression) and functional (VO_{2max}) markers of mitochondrial function suggesting a novel molecular mechanism whereby testosterone might modulate insulin sensitivity in men thus providing an explanation for the association so consistently encountered in epidemiological studies.

While these studies point to a role of testosterone in the development of insulin resistance, another consequence of androgen deprivation therapy might be relevant to an explanation of our observation. In males, the source of oestrogens is androgens (35). Androgen deprivation therapy in men not only is associated with a strong decline of testosterone levels but also of oestrogen levels [36]. A profound oestrogen deficient state, as found in men with aromatase deficiency, appears to be associated with signs and symptoms of insulin resistance and other features of metabolic syndrome [37]. This metabolic state improves or normalizes upon oestrogen administration [38,39]. Therefore, it might not only be the substantial testosterone deficiency but also the associated severe oestrogen depletion, following androgen deprivation therapy, which explains the associated insulin resistance. However, a recent study found no association of between plasma estradiol levels and features of metabolic syndrome [22]. A reduction of plasma estradiol following administration of an aromatase inhibitor (anastrozole) did not impact on insulin sensitivity [40]; so it would seem that metabolic syndrome can only occur with a deep state of oestrogen and androgen deficiency.

Our study revealed a deterioration of biochemical risk factors of cardiovascular disease as a consequence of androgen deprivation therapy. Other studies in non-diabetic men with prostate cancer found an increase in body fat mass, a decrease in lean body mass and an increase in insulin levels associated with an increase in arterial stiffness, substantiating the significance of biochemical risk markers of cardiovascular disease for their pathophysiological implications [41,42]. Low testosterone levels may be an independent risk for morbidity and mortality. This was suggested in a recent study using a USA Veterans Administration clinical database to identify men older than 40 years with repeated testosterone evaluations, without diagnosed prostate cancer [43]. A low testosterone level was a total testosterone level of less than 250 ng/dL (8.7 nmol/L) or a free testosterone level of less than 0.75 ng/dL (0.03 nmol/L). Men were classified as having a low testosterone level (166 (19.3%)), an equivocal testosterone level (equal number of low and normal levels) (240 (28%)), or a normal testosterone level (452 (52.7%)). The risk for all-cause mortality was assessed adjusting for demographic and clinical covariates over a follow- up of up to 8 years. After adjusting for age, medical morbidity and other clinical covariates, low testosterone levels continued to be associated with increased mortality (hazard ratio, 1.88; 95% CI, 1.34–2.63; $P < 0.001$) while equivocal testosterone levels were not significantly different from normal testosterone levels (hazard ratio, 1.38; 95% CI, 0.99% – 1.92%; $P = 0.06$). The authors concluded that low testosterone levels were associated with increased mortality in aging men. Another important recent study assessed whether androgen deprivation therapy was associated with an increased incidence of diabetes and cardiovascular disease in the USA [44]. A population-based cohort of 73,196 Medicare enrollees age 66 years or older who were diagnosed with locoregional prostate cancer during 1992 to 1999 were observed through 2001. More than one third of men received a LHRH agonist. LHRH agonist use was associated with increased risk of incident diabetes (adjusted hazard ratio (HR) 1.44; $P < 0.001$), coronary heart disease (adjusted HR 1.16; $P < 0.001$), myocardial infarction (adjusted HR 1.11; $P = 0.03$), and sudden cardiac death (adjusted HR 1.16; $P = 0.004$). The authors of this study concluded that LHRH agonist treatment for men with locoregional prostate cancer might be associated with an increased risk of incident

diabetes and cardiovascular disease. They recommended that the benefits of LHRH agonist treatment should be weighed against these potential risks.

Obesity not only predisposes to diabetes mellitus and cardiovascular disease, it appears that obesity also constitutes a risk factor to develop a prostate carcinoma [4,5]. Some authors, while confirming this association, have argued that obese men undergo more frequent medical examinations, with an increased chance of having a prostate malignancy diagnosed [6]. In any case, the negative shift that androgen deprivation therapy might produce in the metabolic variables might lead to diabetes and/or cardiovascular disease. The above mentioned case report [7] demonstrated that this is not hypothetical.

The limitations of our study include the small number of patients and its retrospective design. In addition, there was no control population. However, our study functions as an initial exploration, generating hypotheses and justifying further research in this very important medical problem related to treatment of prostate cancer especially in men with diabetes.

In summary, our study shows that androgen deprivation therapy may be associated with worsening in glycaemic control and cardiovascular biochemical risk markers in men with diabetes type II and metastatic prostate cancer. In addition, our study highlights the significance of testosterone, and perhaps of its hormonal derivative estradiol, in the metabolic control. This role of testosterone becomes evident from a host of epidemiological studies. Prostate cancer patients treated with androgen deprivation therapy need to be followed up closely for the possible metabolic consequences of androgen deprivation therapy. This recommendation may be even more important in men with diabetes, obesity and/or cardiovascular disease.

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