Effect of adjuvant androgen deprivation on thyroid function tests in prostate cancer patients

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Androgen deprivation (AD) used in the treatment of prostate cancer is known to alter concentrations of sex hormones and their binding globulins. Less is known as to its effect on thyroid hormones. In this prospective study the effects of AD on thyroid function were clarified. Levels of serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid binding globulin concentrations were measured in prostate cancer patients treated with either radical radiotherapy and androgen deprivation for 12 months (AD) or radical radiotherapy alone (RT). Measurements were made at baseline, and at 3, 6 and 12 months. At baseline and at 3 months the results of thyroid function tests did not differ significantly between groups. A significant decline in serum testosterone in the AD group was accompanied by a significant decline in FT4 at 6 and 12 months, while no significant changes in thyroid function were observed in the RT group. The decline in FT4 among AD patients did not evoke a normal TSH response. Prolonged use of AD hampers the interpretation of thyroid test results. This finding has substantial implications for the follow-up of patients in hormonally treated prostate cancer. ***Anti-Cancer Drugs*** **15:351–356 © 2004 Lippincott Williams & Wilkins.**

Anti-Cancer Drugs. 2004, **15**:351–356

Keywords: androgen deprivation, LHRH analog, prostate cancer, thyroid function

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Received 7 January 2004 **Accepted** 15 January 2004

Introduction

Prostate cancer is the most common cancer among men and the second commonest cause of male cancer death in Western countries. Survival increases in the 1990s were due to both earlier diagnosis and improved therapeutic approaches, especially androgen deprivation therapy (AD) [1]. During recent years it has become common practice to combine AD with radical radiotherapy in a neoadjuvant setting, since this approach has been shown to improve the survival of patients with poor prognosis [2,3]. Long-term adjuvant hormonal therapy (more than years) has become the standard for patients diagnosed with a Gleason score of 8 or above [3]. AD has also been proposed as an alternative to watchful waiting for men with clinically localized prostate cancer electing less aggressive management and it is widely used as a means of preventing progression if local therapies cannot be utilized for reasons of patient preference or poor general condition [4].

AD therapy for prostate cancer is known to affect the plasma concentration of several hormones [5,6]. A significant impact of estrogen treatment after orchiectomy on thyroid hormones has been reported [7]. Less is known of the effect on thyroid function tests of androgen deprivation with LHRH analogs on thyroid function tests. We prospectively studied thyroid hormone levels during 12 months of adjuvant AD treatment with radiotherapy-treated patients as controls.

Patients and methods

The prospective study involved patients treated with curative intent with radiotherapy between January 1999 and June 2001 at the Department of Radiotherapy and Oncology, Turku University Hospital. Only patients with newly diagnosed prostate cancer requiring radiotherapy to the prostate were accepted. The patients had to fulfill at least two of the following criteria to be eligible for AD treatment: tumor grade ≥ 2, Gleason ≥ 5 and/or PSA $\geq 20\,\mu g/l$. The control group (RT) was treated with radical radiotherapy alone. Clinical characteristics of the patients are presented in Table 1. None had a history of use of corticosteroids, thyroid disease, liver disease or any endocrine disorders.

AD was given for 12 months using 3-monthly depot injections of LHRH analog, commenced 2 months prior to radical radiotherapy. AD therapy was started with flutamide 250 mg 3 times a day given for 4 weeks; LHRH analog (11.25 mg s.c. q3 months 4 times) was added after 2 weeks. AD therapy lasted 12 months.

Radiotherapy was given by the conformal technique using 15 MV photons/Varian Clinac 2100C/D linear accelerator

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Table 1 Characteristics of prostate cancer patients with AD and RT with curative intention

Variable	AD ($N=35$)	RT ($N=36$)	p
Age [years, mean (SD)/range]	69 (6.4)/48–77	69 (6.7)/48–79	0.395
Performance status (WHO) [mean (range)]	0.7 (0–2)	0.7 (0–2)	
PSA at baseline [mean (SD)]	22 (34)	9 (7)	0.009
Tumor stage			<0.001
T1	0	7	
T2	5	22	
T3	26	7	
T4	4	0	
N+	2 (T3)	0	
Histologic grade			0.004
1	7	21	
2	17	10	
3	11	5	

p values for difference between groups in t-tests and χ^2-test.

(Varian, Palo Alto, CA) to a mean tumor dose of 69 Gy (SD 3.15, range 61–77 Gy). No fixation was used. Portal images were taken with a Varian Portal Vision Mark 2 electronic portal imaging device, integrated with Varis Vision 5.0 software, on average once a week during about 7 weeks of irradiation.

Laboratory methods

Serum samples for hormone analysis were collected prior to treatment, and at 3, 6 and 12 months, and stored at −70°C. Samples were taken before early afternoon to avoid diurnal variation. The analysis was made using the DELFIA system for measurement of thyroid hormones, and in one session with the same kits for the samples collected, using commercially available kits (Wallac Perkin-Elmer, Turku, Finland) as follows.

Human thyroid stimulating hormone (hTSH) ultra has a functional sensitivity below 0.007 U/ml. The AutoDELFIA hTSH assay is a solid-phase two-site fluoroimmunometric assay, based on the direct sandwich technique in which three monoclonal antibodies (derived from mice) are directed against separate antigenic determinants of the hTSH molecule. Assays of hTSH levels are important in the investigation and diagnosis of the hypothalamus–pituitary–thyroid axis. High-sensitivity hTSH can discriminate between euthyroid and hyperthyroid patients, and permits distinction between mildly subnormal and frankly hyperthyroid hTSH values. Analysis range was 0.005–100 Ug/ml (clinical normal range 0.4–4.5 mU/l). Precision of the AutoDELFIA TSH Ultra assay varies between 6 and 3% CV when standard concentrations are between 0.03 and 100 U/ml.

Free thyroxine (FT4) is a non-analog, backtitration assay based on the theoretically optimum design. The validity of the DELFIA FT4 assay has been shown to be *independent of serum protein levels*. Determination of free thyroxine in serum is an important parameter in assessing thyroid function. In hypothyroidism the serum concentration is generally depressed; in hyperthyroidism, generally elevated. The AutoDELFIA FT4 assay is a solid-phase time-resolved fluoroimmunoassay, based on the back-titration principle and using second antibody separation. Analysis range for free T4 was 2–80 pmol/l (normal range 9.6–17.1 pmol/l). Precision of the AutoDELFIA FT4 assay is less than 3% when standard concentrations are between 3.6 and 81.

Thyroid binding globulin (TBG) is a glycoprotein which serves as the principal serum carrier for T4 and triiodothyronin (T3). The affinity to T4 is 2–10 times greater than that to T3. The AutoDELFIA TBG assay is a solid-phase time-resolved fluoroimmunoassay based on competition between europium-labeled TGB and sample TBG for a limited amount of binding sites on TBG-specific monoclonal antibodies (derived from mice). Analysis range for TBG was 0.7–80 mg/l. Precision of the AutoDELFIA TBG assay is less than 3% CV when standard concentrations are between 5.5 and 81 mg/l.

Testosterone and *estradiol* were determined by the Auto DELFIA assay. The analysis range for testosterone was 0.4–50 nmol/l (normal range 10–33 nmol/l). For estradiol the range was 50–15 000 pmol/l (normal value for men below 114 pmol/l). Precision of the AutoDELFIA Testosterone assay varies between 5 and 3% CV when standard concentrations are between 0.38 and 63.6 nmol/l. Precision of the AutoDELFIA Estradiol assay varies between 10 and 3% CV when standard concentrations are between 0.05 and 15 nmol/l.

The mean values for each measured variable were not significantly different for two separate laboratory batch runs in which measurements were made.

Statistical analyses

The data were summarized showing mean values and SE. Statistical comparisons of the AD and RT groups at baseline were made using two-sample t-test or χ^2-tests as appropriate. Analysis of variance for repeated measurements was used to compare the groups with respect to changes in hormone levels: (i) difference between study

groups, (ii) the time effect, i.e. change during follow-up periods, and (iii) interaction between group and time effect. Dependent variables were logarithmically transformed to reach required assumptions of normality. In further analysis the differences between baseline and other periods were studied using paired *t*-tests, with Bonferroni correction for *post hoc* comparisons. The analyses were performed using the MIXED procedure in the SAS System for Windows, release 8.02/1999. *p* values less than 0.05 were considered statistically significant.

Results

The patient groups differed in some pretreatment cancer parametrics, since indications for hormonal therapy were formulated to treat with AD patients with poor prognostic characteristics. However, no statistically significant differences were observed between the groups in age, pretreatment performance status (Table 1) or any baseline hormone levels. Hormone values are presented for AD patients in Table 2(a) and for RT patients in Table 2(b). At baseline, the AD and RT groups had comparable mean values for FT4 ($p = 0.58$), TSH ($p = 0.46$), TBG ($p = 0.99$), and testosterone and estradiol ($p = 0.73$), these being within normal ranges.

Figure 1 shows testosterone levels by group with a statistically significant decrease by 3 months from baseline in the AD group ($p < 0.0001$). The levels in the radiotherapy group remained within normal range. The interaction between group and time was statistically significant ($p < 0.001$).

Table 2(a) presents mean values for serum testosterone and thyroid hormones among AD patients at baseline, and results of longitudinal testing at 3, 6 and 12 months. A significant decrease of testosterone to castration level occurred among AD patients by 3 months and continued throughout the study period. This was accompanied by a statistically significant fall in estradiol from 0.09 ± 0.03 to 0.03 ± 0.02 ($p > 0.001$). There followed a significant PSA response, with 92% of AD patients showing PSA values less than 1 g/l at 12 months, while the corresponding figure in the RT group was 81%.

A statistically significant decrease was observed in the FT4/TBG ratio from baseline values of 0.72 ± 0.145 to 0.64 ± 0.145 at 6 months ($p < 0.001$) and to 0.66 ± 0.16 at 12 months ($p < 0.001$). This fall was due mainly to a decrease in FT4 levels from 12.4 ± 0.149 to 11.7 ± 1.75 at 6 months ($p = 0.008$) and to 11.4 ± 1.74 at 12 months ($p = 0.001$). Serum TBG and TSH levels showed no statistically significant changes during the observation period.

As presented in Table 2(b) for the radiotherapy group, serum testosterone declined significantly after radical radiotherapy, from 14.7 ± 5.98 to 12.7 ± 6.07 at 12 months ($p < 0.025$). However, the magnitude of change was much less substantial among RT patients than among patients treated with AD and there was no statistically significant change in serum estradiol from baseline to 12 months ($p = 0.12$). Corresponding thyroid hormone levels remained without statistically significant changes in the RT group. Serum TBG levels did not undergo statistically significant changes during the observation period.

No statistically significant changes were observed in TSH levels in either group during the 12 months.

Figure 2 shows free T4 levels by treatment group, with a statistically significant decrease in the AD group from baseline to 6 ($p = 0.008$) and 12 months ($p < 0.001$). The interaction between group and time was statistically significant ($p < 0.004$).

Discussion

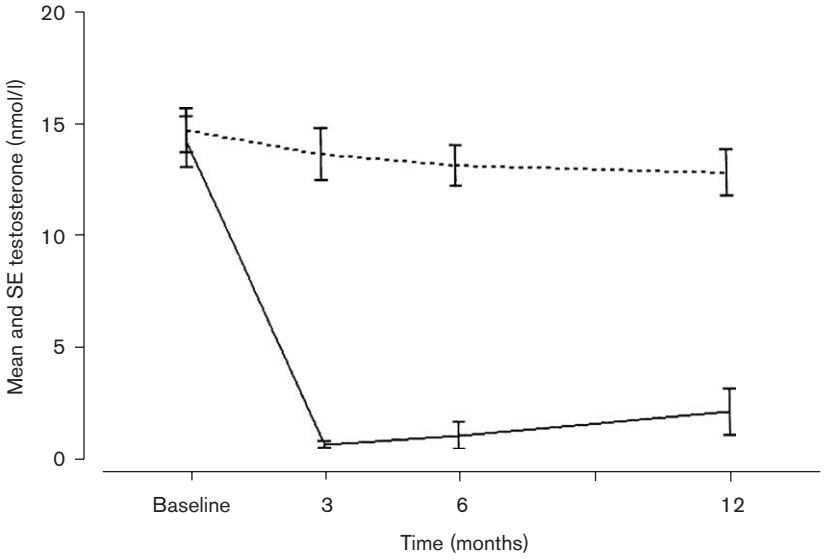
The increasing use of AD in prostate cancer suggests a need for additional studies on its metabolic effects. The data presented here clarify the effects of LHRH on serum thyroid hormone concentrations in prostate cancer patients and improves understanding of the effects of AD. The patients in the present study with 12 months' follow-up remained eumetabolic, but evinced a

Table 2 Hormonal changes in the AD group during treatment expressed as means (SD)

	Baseline	3 months	6 months	12 months	*p*
(a)					
testosterone (nmol/l)	14.1 (6.8)	0.59 (0.76)	0.99 (3.35)	2.03 (5.67)	<0.001
TSH (μU/ml)	1.39 (0.67)	1.42 (0.75)	1.31 (0.61)	1.51 (1.20)	0.514
FT4 (pmol/l^2)	12.4 (0.149)	11.9 (1.73)	11.7 (1.75)	11.4 (1.74)	0.001
TBG (mg/l)	17.6 (2.5)	18.1 (3.0)	18.6 (2.4)	17.5 (2.5)	0.195
FT4/TBG	0.72 (0.145)	0.69 (0.18)	0.64 (0.145)	0.66 (0.16)	0.004
(b)					
testosterone (nmol/l)	14.7 (5.98)	13.6 (6.82)	13.1 (5.21)	12.7 (6.07)	0.025
TSH (μU/ml)	1.79 (3.09)	1.63 (2.31)	1.88 (2.42)	1.68 (1.77)	0.056
FT4 (pmol/l^2)	12.7 (2.48)	12.3 (2.45)	12.4 (2.16)	12.9 (2.33)	0.081
TBG (mg/l)	17.6 (2.8)	17.1 (2.8)	17.2 (3.2)	17.0 (3.7)	0.219
FT4/TBG	0.75 (0.23)	0.75 (0.28)	0.76 (0.25)	0.80 (0.29)	0.079

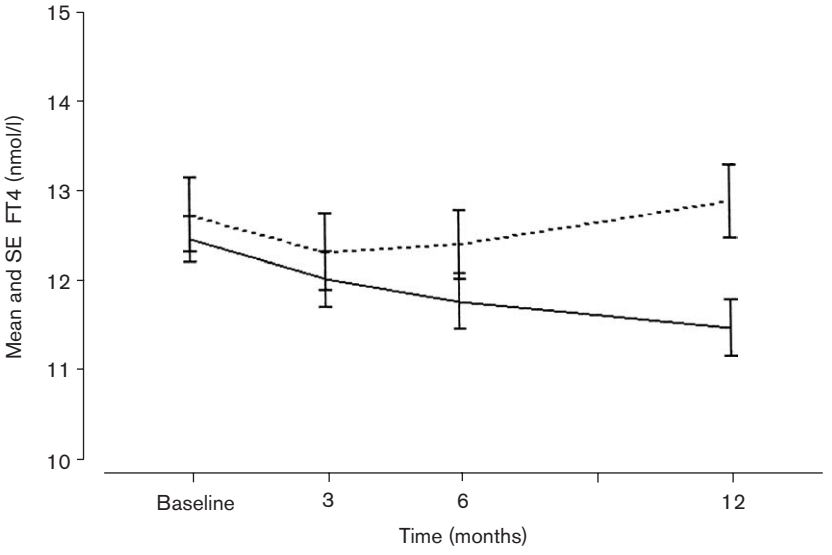
Values for the time effect during the periods (a) and in the RT group during treatment (b). *p* values for the time effect during the periods.

Fig. 1



Testosterone levels from baseline to 12 months for prostate cancer patients treated with AD (solid line) or RT (dashed line).

Fig. 2



FT4 levels from baseline to 12 months for prostate cancer patients treated with AD (solid line) or RT (dashed line).

significant decrease in FT4. Changes of thyroid function during AD have practical clinical applications for the follow-up of these patients. Clinicians need to be able to identify factors making for alterations in thyroid function tests when related changes are to be expected.

AD caused a rapid fall in serum testosterone, which remained at castration level throughout the study. The fall observed in the RT group accorded with an earlier report on radiotherapy effects [9]; although statistically significant it did not reach castration level. The fall in testosterone in AD group was accompanied by a marked PSA response and most patients had undetectable PSA levels at 12 months. The progressive decrease in FT4 with continued AD cannot thus be explained by the AD patients' more advanced cancer. However, their quality of

life was worsened, especially physical function, since fatigue and diarrhea increased significantly with continuing AD [10]. This may have contributed to the fall in FT4 but does not explain the absence of TSH response. Normally, a decrease in FT4 is followed by a rise in TSH, which corrects the FT4 level. This did not take place among AD patients. A normal TSH may be recorded in patients with profound hypothyroidism secondary to pituitary or hypothalamic disease [11].

A previous small study with six prostate cancer patients indicated that TSH remained unchanged after 3 months on anti-androgens [12]. The present study showed likewise no statistically significant changes in TSH or other thyroid hormones at 3 months and even stable TSH throughout the AD treatment. The absence of a TSH response to falling FT4 levels at 6 and at 12 months in the AD group may indicate a suppressive effect of LHRH analog on central TSH regulation or a direct decreasing effect on the production of free thyroxin. This distorts the interpretation of thyroid function tests. In clinical practice when thyroid function is evaluated, patients are first tested for TSH, and if this is indicative of thyroid malfunction, changes are consequently to be expected on FT4. The important finding in the present study was that patients on AD may show normal TSH values although FT4 is decreased, because AD seems to suppress the normal TSH response. The assessment of free thyroid hormone levels is regarded as the most reliable means of interpreting thyroid function during hormonal manipulation [13]. In the present analysis of free T4 the methodology was not influenced by serum protein levels, which excludes the possibility of artifact findings.

Thyroid hormone–plasmaprotein interactions are of two general types [13]; a primary alteration in the concentration of thyroid hormones in the blood, such as occurs with hypothyroidism or thyreotoxicosis, and pathologic factors affecting the thyroid gland determine rates of thyroid hormone secretion independent of any pituitary influence; in the second type, disordered binding interactions result from primary alterations in the concentration of TBG. Observations on prostate cancer patients have shown that TBG levels may be influenced by estrogen treatment [7,14] and, accordingly, at 6 months TBG became slightly elevated in the AD patients. The interpretation of TBG during hormonal manipulation is difficult [13]. TBG can be affected by liver diseases [13], which were excluded in the present cohort. A fall in testosterone is likely to cause a rise in TBG, which is counterbalanced by the simultaneously falling estradiol. An increase in TBG will initially increase the concentrations of total serum thyroid hormones and, following the TBG increase, FT4 will be decreased [13]. Central hypothyroidism is characterized by normal TSH levels while FT4 is lowered [15]. Although LHRH analog should act selectively on LH receptors only, a simultaneous effect on TSH regulation cannot be excluded on the basis of the present results. The findings here indicate a need to establish whether the suppressive effect of LHRH analog on pituitary regulation is not limited to LH receptors but also affects TSH and thyroid hormone regulation.

Deterioration in the physical quality of life can also cause a fall in FT4, but cannot explain the absence of TSH response. Patients treated with AD often suffer from a deterioration in quality of life, with symptoms of depressive mood, fatigue and weight gain [16], all of which may be interpreted as 'normal' consequences of AD. Similar symptoms, however, can be caused by thyroid dysfunction. This should be acknowledged when prostate cancer patients are treated with AD for longer periods.

Central effects of AD have been suggested in previous reports [10,17,18], but the issue of pituitary changes and their possible association with production of TSH response requires further studies. The patients on AD gain weight and develop impaired quality of life which results in decreased physical activity [10]; the role of these on thyroid function needs to be clarified.

An increase in serum tri-iodothyronine (S-T3) in men with prostate cancer compared to those with benign hyperplasia or normal prostate has recently been reported [19]. S-T3 was not included in the present analysis, since its potential addition of information in thyroid function diagnostics is limited to hyperthyreosis [15].

The results indicate that thyroid function and its diagnostics may be affected by AD treatment. With the increasing use of AD in prostate cancer, recognition of this finding is important. Even short-duration AD is known to cause a long-lasting decline in serum testosterone especially among patients with low baseline hormone levels [20]. With the prolonged AD, further studies are needed to clarify its effects on thyroid hormones and the possible clinical significance of such findings. Clinicians should be able to identify alterations in thyroid function tests in these patients to exclude conditions such as hypothyroidism, which can be easily treated with significant improvement in quality of life for the patient. The effects of AD on thyroid function could be further clarified by TRH tests and follow-up values after AD.

Conclusion

In conclusion, AD for 6 months and over in prostate cancer patients results in a significant decrease in FT4 and failing TSH response. This indicates a need for further studies on thyroid function when AD is used in adjuvant indications and when its duration is extended over several years, as recommended for patients with poor prognosis. Although the patients here remained

eumetabolic, the regulation of thyroid function and the interpretation of diagnostic tests was affected. These results have substantial implications for the follow-up of patients treated with AD.

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