Effect of androgen deprivation therapy in the thyroid function test of patients with prostate cancer

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We have assessed the effect of androgen deprivation therapy (ADT) in the thyroid function test in prostate cancer patients. Serum levels of tri-iodothyronine (T3), thyroxine (T4), free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were determined in a cross-sectional study that included 279 patients diagnosed with prostate cancer. A subset of 96 patients free of prostate-specific antigen relapse after radical prostatectomy became a control group and 183 patients under continuous ADT formed the study group. Sixty-four patients out of the study group were treated with luteinizing hormone-releasing hormone (LHRH) agonist and 119 with LHRH agonist plus bicalutamide. The average time of ADT was 42.5 months (3–218). Results were as follows. Mean T3 level was 122.7 ng/dl (72.6–213.0) in the control group and 123.8 ng/dl (64.4–228.2) in patients under ADT, $p=0.472$. Mean T4 level was 7.66 (1.81–4.30) and 7.66 μg/dl (3.60–13.30), respectively, $p=0.884$. Mean TSH level was 1.58 (0.44–11.70) and 1.81 mU/dl (0.15–6.58), respectively, $p=0.007$. Mean FT4 level was 1.24 (0.80–1.90) and 1.18 ng/dl (0.80–1.90), respectively, $p=0.018$. No statistically significant differences between the T3, T4, TSH and FT4 serum levels were detected according to the modality of ADT. The serum level of TSH was higher than 5 mU/l in six patients (2.1%); however, all cases had a normal FT4 serum level. This mild hypothyroidism was detected in two of the 96 patients of the control group (2.1%) and in four of the 183 under ADT (2.2%). Our data show that ADT seems to alter the thyroid function test. A statistically significant increase in TSH serum level and a decrease in FT4 serum level were detected in patients under ADT. However, only a mild hypothyroidism was detected in about 2% of the patients with prostate cancer, independently of ADT. *Anti-Cancer Drugs* 16:863–866 © 2005 Lippincott Williams & Wilkins.

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Introduction

Prostate cancer is the most common cancer among men and the second cause of male cancer death in Western Europe [1]. Earlier diagnosis and improved therapeutic approaches seem to have contributed to the increase in survival observed during the 1990s. A higher use of androgen deprivation therapy (ADT) has also been related to the increase in survival [2]. Initial data suggested an improvement in outcome in those patients who received concomitant ADT after radiation of higher-stage tumors [3]. During the last few years it has become common practice to combine ADT with radical radiotherapy in a neoadjuvant setting, since this approach has been shown to improve the survival of patients with poor prognosis [4]. Long-term adjuvant hormonal therapy has become the standard for patients diagnosed with a Gleason score of 8 or above [5]. Cooperberg *et al.* documented a great rise in the use of ADT from 1989 to 2001. Most significant was the increased use of ADT together with external beam radiotherapy, from 9.8 to 74.6% of patients [6]. Also contributing to the increased use of luteinizing hormone releasing hormone (LHRH) agonists are data suggesting a survival advantage for the early use of LHRH agonist therapy for men with metastatic prostate cancer [7]. Finally, ADT 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 [8].

In light of the increasing use of the longer-acting forms of medical castration, it is important for the treating physician to be familiar with the potential complications and side-effects of these agents. Physicians can then counsel their patients about these side-effects as well as institute measures to prevent many of the complications associated with the use of these agents [9]. Recently, there has been information objectively detailing the

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influence of ADT on memory, cognition and other non-specific effects [10,11]. ADT affects the plasma concentration of several hormones [9]. However, less is known about the effect of ADT on thyroid function [12]. From our point of view, it would be important to know if thyroid function is altered by ADT. Some of these side-effects of ADT could be consistently related to a mild or subclinical hypothyroidism. Patients with mild hypothyroidism are often identified through routine screening or in the course of an evaluation of common non-specific symptoms or hypercholesterolemia [13]. If this could be demonstrated, these side-effects could be treated or even prevented.

Materials and methods

A cross-sectional study performed between January 2000 and December 2002 involved 279 patients with previous histological diagnosis of prostate cancer. A subset of 96 patients, with clinically localized prostate cancer submitted to radical prostatectomy alone and free of biochemical relapse, were selected as a control group. Another subset of 183 patients, under continuous ADT, became the study group. All patients under ADT were free of biochemical or clinical relapse at the time of this study. The modality of ADT was medical castration with 3 months depot LHRH agonist in 64 patients and maximal androgen blockade (MAB) with 3 months depot LHRH agonist plus bicalutamide (50 mg/day) in 119 patients. The median age of the entire group was 70 years (53–89) and the mean follow-up of the patients under ADT was 42.5 months (3–218). Patients of the control group and the study group were age matched. Moreover, patients under castration and those receiving bicalutamide were under ADT for a similar period of time, i.e. 42.2 and 42.6 months, respectively.

Serum samples for thyroid test determination were collected at the same time of routine control of serum prostate serum antigen and testosterone. All the analyzed thyroid hormones were determined by an automated chemiluminescent assay (Bayern Inc., New York, USA). The normal range of serum tri-iodothyronine (T3) was 60.0–181.0 ng/dl. The normal range of serum thyroxine (T3) was 4.50–10.90 μg/dl. The normal range of free thyroxine (FT4) was 0.80–1.80 ng/dl. Finally, the normal range of serum thyroid-stimulating hormone (TSH) was 0.35–5.00 mU/l.

Values of serum thyroid levels were expressed as mean and 95% confidence interval of the mean. Statistical analysis was performed using the non-parametric Mann–Whitney *U*-test to compare means and the χ^2-test to compare distributions of qualitative variables. SPSS version 12 was used in this analysis.

Results

The serum levels of thyroid hormones in patients who did not receive ADT and levels in patients under ADT are presented in Table 1. The serum levels of T3 and T4 were similar in both groups, $p > 0.05$. However, we observed a statistically significant decrease of FT4 in patients under ADT, $p = 0.018$. Moreover, a statistically significant increased level of TSH was observed in those patients under ADT, $p = 0.007$. We also analyzed the behavior of serum thyroid hormones according to the modality of ADT. The distribution of these levels corresponding to the patients under MAB or under LHRH agonist is presented in Table 2. We did not detect statistically significant differences between the serum thyroid test levels observed in patients under ADT and in those who did not receive ADT, $p > 0.05$.

We analyzed the distribution of the qualitative levels of serum thyroid hormones according to the normal ranges established in our laboratory. We detected 97.8% of the patients in the normal range of T3 levels and six patients (2.2%) with levels slightly high. In 93.5% of the patients the serum levels of T4 were in the normal range; slightly

Table 1 **Serum levels of thyroid hormones in patients under ADT and those without androgen suppression**

Serum concentration	Without ADT		With ADT		*P*
	Mean	(95% CI)	Mean	(95% CI)	
T3 (ng/dl)	122.7	(116.5 – 128.9)	123.8	(120.1 – 127.4)	0.472
T4 (μg/dl)	7.66	(7.29 – 8.03)	7.67	(7.41 – 7.92)	0.884
FT4 (ng/dl)	1.24	(1.19 – 1.29)	1.18	(1.15 – 1.21)	0.018
TSH (mU/l)	1.58	(1.31 – 1.85)	1.81	(1.65 – 1.96)	0.007

Table 2 **Serum levels of thyroid hormones in patients under ADT according to the modality of ADT**

Serum concentration	MAB		LHRH agonist		*P*
	Mean	(95% CI)	Mean	(95% CI)	
T3 (ng/dl)	122.1	(117.7 – 126.6)	126.8	(120.5 – 133.1)	0.385
T4 (μg/dl)	7.68	(7.34 – 8.02)	7.65	(7.25 – 8.04)	0.716
FT4 (ng/dl)	1.18	(1.14 – 1.21)	1.19	(1.13 – 1.25)	0.931
TSH (mU/l)	1.92	(1.72 – 2.12)	1.72	(1.38 – 1.82)	0.117

low levels were detected in six patients (2.2%) and slightly high ones in 13 (4.7%). In relation to the serum levels of FT4, 98.6% of the patients had normal levels and four patients (1.4%) had slightly high levels. Finally, 97.1% of the patients had normal levels of TSH; two patients (0.7%) had levels slightly low and six patients (2.1%) had levels over the normal range. We remark that no patient had a level of FT4 under the normal range and only six patients (2.1%) had slightly high levels of TSH. Mild hypothyroidism is considered when the serum TSH level is higher than 5 mU/l and serum FT4 is in the normal range [13]. Table 3 shows the serum levels of TSH and the corresponding FT4 levels in those patients with serum TSH higher than 5 mU/l. Out of these six patients with serum TSH higher than 5 mU/l, four patients were under ADT (2.2%) and two patients were without ADT (2.1%). All of these patients had normal FT4 serum levels.

Finally, the distribution of serum FT4 and TSH according to the treatment of ADT and the follow-up of this treatment is represented in Figure 1. A significant decrease of serum FT4 is observed during the first 12 months of ADT and thereafter slight fluctuations are observed. On the other hand, during the first 12 months of ADT, a significant increase of serum TSH is observed, and thereafter a stabilization and a small decrease after 24 months.

Table 3 Serum level of TSH and FT4 and ADT in the group of six patients in whom TSH was over the normal range

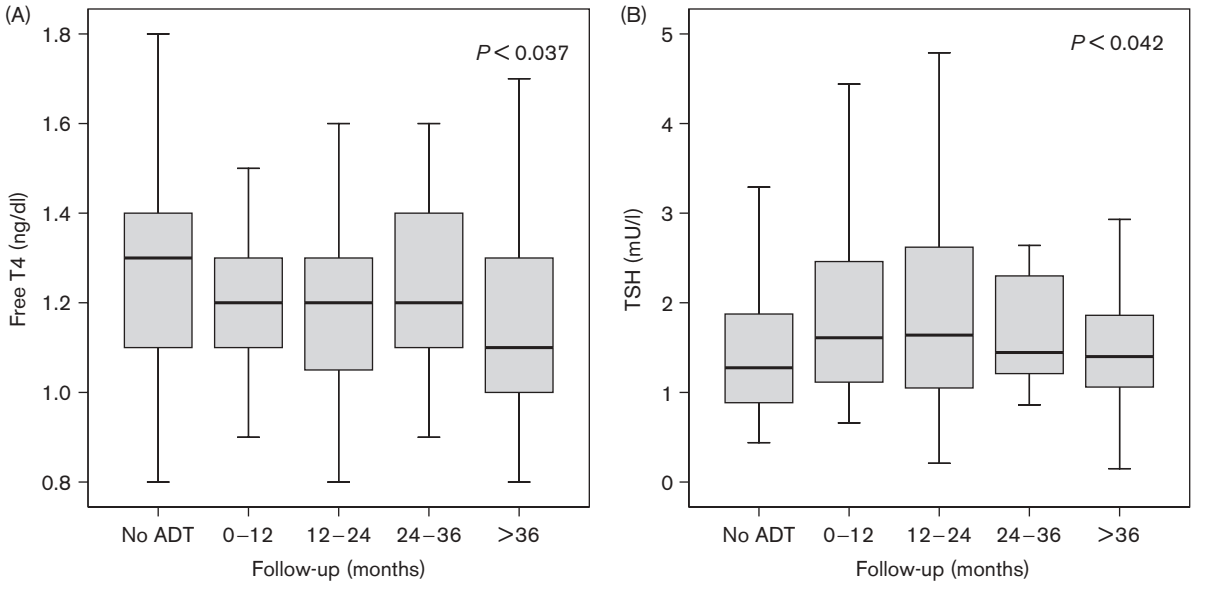
Case	TSH (0.35 – 5.00 mU/l)	FT4 (0.80 – 1.80 ng/dl)	ADT
1	5.03	1.21	Yes
2	5.17	1.24	Yes
3	5.20	1.11	Yes
4	5.58	1.40	No
5	6.58	0.92	Yes
6	11.70	1.13	No

Discussion

Recently, there has been objective information detailing the effect of ADT on memory and cognition, symptoms of depressive mood, fatigue, weight gain, and overall deterioration in quality of life [10–12,14–16]. Some of these symptoms would be consistently related with a secondary hypothyroidism [12].

A significant impact of estrogen treatment on thyroid hormones after orchidectomy has been reported [17]. However, less is known of the effect on the thyroid function test of androgen deprivation with LHRH agonist. A previous small study with six prostate cancer patients indicated that TSH remained unchanged after 3 months on LHRH agonist [18]. Salminen *et al.* [12] have recently studied the effects of ADT on thyroid function in a prospective study. Levels of serum TSH, FT4 and thyroid-binding globulin concentrations were measured in 71 prostate cancer patients treated with either radiotherapy and ADT for 12 months in 35 patients or radiotherapy alone in 36 patients. Measurements were made at baseline, and at 3, 6 and 12 months. At baseline

Fig. 1



Levels of FT4 (A) and TSH (B) according to the ADT treatment and its length. Levels represented in the boxes include the 50th percentile and the line represents the median.

and at 3 months, the results of thyroid function tests did not differ significantly among the groups. The significant decline in serum testosterone in the ADT 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 group of patients treated with radiotherapy alone. The decline in FT4 among ADT patients was not accompanied with an increase of TSH. In the opinion of these authors, the absence of a TSH response to falling FT4 levels at 6 and 12 months in the ADT group could indicate a suppressive effect of LHRH agonist on central TSH regulation or a direct decreasing effect on the production of FT4. This distorts the interpretation of the thyroid function test. In clinical practice, when the 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.

A statistically significant decrease in the mean serum concentration of FT4 was observed in this study, as Salminen *et al.* also did [12]. Moreover, we found a statistically significant increase in the mean serum concentration of TSH. We also observed that the decrease of serum FT4 and the increase of TSH happened during the first 12 months of ADT, again as Salminen *et al.* did [12]. However, we only observed a TSH serum level higher than 5 mU/l in four of the 183 patients under ADT (2.2%) and in two of 96 patients without ADT (2.1%). In all of these patients the serum level of FT4 was in the normal range.

Mild hypothyroidism is a common syndrome, defined by an isolated increase of serum thyrotropin level in the setting of normal serum thyroid hormone levels, in the presence or absence of symptoms [13]. The worldwide prevalence of mild or subclinical hypothyroidism ranges from 1 to 10% [13]. The results of this study are consistent with the hypothesis that ADT can alter the thyroid function test during the first 12 months of treatment, as Salminen *et al.* have proposed [12]. However, we failed to demonstrate a clinically significant impact of ADT on serum levels of FT4 even in the six patients with an increased TSH serum level. Unfortunately, Salminen *et al.* did not provide information about the qualitative serum levels of the analyzed thyroid function test [12].

Conclusion

A statistically significant increase of serum TSH and a statistically significant decrease in serum FT4 was observed in patients under ADT. These findings suggest that ADT could alter the thyroid function test. However, we doubt the clinical meaning of these findings because we only detected a mild hypothyroidism at a rate in the range previously defined in the literature [12]. Moreover, the rate of mild hypothyroidism detected in this study was similar in the cohort of patients under ADT and in those patients who did not receive ADT. At present, the screening of hypothyroidism is controversial; however, it seems quite reasonable in men over 65 years [12]. We can conclude that a prospective study would be necessary in order to fully investigate the real influence of ADT in the thyroid function test as well as its possible relationship with some of the unspecific side-effects related to ADT.

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