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Prostate Specific Antigen Levels in Animal Model of Andropause Undergoing Testosterone Propionate Replacement Therapy – Experimental Study

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ABSTRACT

Introduction: The most undesired reaction at testosterone therapy is the potential risk of induction of clinically manifested prostate disease. Most, but not all of the thorough studies don't find statistically significant relation between the endogenic level of testosterone and the development of BPH (Benign Prostate Hyperplasia) and prostate cancer. In some tests the levels of serum PSA (Prostate Specific Antigen) are slightly increased, but in the normal borders (below 4 ng/ ml). The potential benefits and the possible risks at the testosterone replacement therapy of aged men must be juxtaposed. They are based mostly upon clinical studies over the effects of testosterone replacement in a lot of androgen deficient hypogonadial men, and upon scarce number of control trials with aged men and experimental models. Aim: To study the dynamics in the levels of serum testosterone and PSA during replacement therapy with testosterone propionate in dose 4 and 8 mg/kg body weight (BW). Material and method: Orchiectomized, sham operated and aged male rats were used, in a condition of acute and chronic treatment (15 days, 15 weeks). The levels of serum testosterone and PSA were prosecuted. Results and discussion: Testosterone propionate, applied on rats with androgen deficiency at 8mg/kg BW dose restores the physiologic levels of the total testosterone does not change the values of PSA. The supplementation with testosterone propionate increased its levels with significance at the higher dose. A rise in the serum levels of testosterone is also observed at the aged male rats, as a result of the application of its propionate salt. Significance resulted from the chronic use of dose 8 mg/kg BW. Conclusion: The results of the current experimental studies show that, both at orchiectomized and at aged male rats the application of testosterone propionate for 15 days or 15 weeks doesn't change the level of PSA towards controls. Furthermore-in all the tested animals its value is zero.

KEYWORDS : andropause, testosterone propionate, prostate specific antigen

Introduction. The most serious undesired reaction to testosterone therapy is the potential risk for induction of clinically manifested prostate disease. Most of, but not all of the thorough studies do not find statistically significant relation between the endogen level of testosterone and the development of BPH and prostate cancer. In some studies the serum PSA levels are slightly increased, but are still in the normal borders (below 4 ng/ml) .

It must be taken into consideration the fact that the total number of testosterone treated men and the duration of the therapy have been limited and the studies have no statistic authenticity for evaluation of the long-term risks for appearance of BPH and prostate cancer. Thorough experimental studies must be carried out in order to determine the influence of testosterone over the prostate and to make the risks and the benefits of this therapy clear.

When testosterone replacement is concerned the potential benefits and the possible risks must be juxtaposed. They are based mostly upon clinical studies over the effects of testosterone replacement at a lot of androgen deficient hypogonadial men and over very small number controlled trials with aged men and experimental models.

Material and method:

140 male Wistar rats were used, weight from 270 to 380 grams. The design of the experiment is approved by the Bulgarian Drug and Food Agency (License №21/19.03.2012) and decision of the Local Ethical Committee at MU Plovdiv, protocol №3/25.07.2012. The animals are distributed in groups (Table 1).

Table 1. *Groups Description*

Група	Легенда	Описание
1.	KMX	Control group young castrated animals
2.	COX	SHAM operated chronic treated young animals
3.	MX4	Young, chronic treated animals with testosterone 4 mg/kg b.w.
4.	MX8	Young, chronic treated animals with testosterone 8 mg/kg b.w.
5.	KCX	Control group chronic old treated animals
6.	CX4	Old, chronic treated animals with testosterone 4 mg/kg b.w.
7.	CX8	Old, chronic treated animals with testosterone 8 mg/kg b.w.
8.	KMO	Control group young, castrated, acute treated animals
9.	MCO	SHAM operated, acute treated animals
10.	MO4	Young, acute treated animals with testosterone 4 mg/kg b.w.
11.	MO8	Young, acute treated animals with testosterone 8 mg/kg b.w.
12.	CO4	Old, acute treated animals with testosterone 4 mg/kg b.w.
13.	CO8	Old, acute treated animals with testosterone 8 mg/kg b.w.
14.	KCO	Control group old, acute treated animals

The young animals in this experimental study are 6 months old with average weight 275±5,1grams. The old rats are above 3 years old with average weight 376 ± 6,2 grams. After previously carried out castration or simulative operation and acclimatization of 14 days the rats are injected i. m. (back thigh muscle, gluteus) once a week, as follows (Table 2).

Table 2. *Experimental design*

Group	Abbrev.	N	Treatment	Duration
1.	COX	10	0,5 ml Oleum helianti (Sopharma)	15 weeks
2.	KMX	10	0,5 ml Oleum helianti (Sopharma)	15 weeks
3.	MX4	10	4 mg/ kg b.w Testosterone propionate (Sopharma)	15 weeks
4.	MX8	10	8 mg/ kg b.w Testosterone propionate (Sopharma)	15 weeks
5.	KC	10	0,5 ml Oleum helianti (Sopharma)	15 weeks
6.	CX4	10	4 mg/ kg b.w Testosterone propionate (Sopharma)	15 weeks
7.	CX8	10	8 mg/ kg b.w Testosterone propionate (Sopharma)	15 weeks
8.	KMO	10	0,5 ml Oleum helianti (Sopharma)	15 days
9.	MCO	10	0,5 ml Oleum helianti (Sopharma)	15 days
10.	MO4	10	4 mg/ kg b.w Testosterone propionate (Sopharma)	15 days
11.	MO8	10	8 mg/ kg b.w Testosterone propionate (Sopharma)	15 days
12.	CO4	10	4 mg/ kg b.w Testosterone propionate (Sopharma)	15 days

13.	CO8	10	8 mg/ kg b.w Testosterone propionate (Sopharma)	15 days
14.	KCO	10	0,5 ml Oleum helianti (Sopharma)	15 days

During the experiment all the animals were bred in standard laboratory conditions. Air temperature 26 ± 1°C, relative humidity 65 ± 5%, free access to food and tap water.

Blood collection was gathered through decapitation under ether narcosis, bellow glass bell filled with vapors of diethyl ether for 60 seconds. The samples received are sent immediately in the Department of Clinical Laboratory at MU Plovdiv. Total testosterone is tested trough ELISA kit of DRG International, USA cat. № EIA – 1559 with analyzer: SIRIO – microplate reader, SEAC, ITALY. The PSA was observed MEIA kit from Abbott Laboratories USA with cat. number 3C19 on AxSYM™ system.

Statistical analyses were carried out with package SPSS 22.0 (Statistical Package for Social Science) for Windows 8.1. For all of the indexes is calculated average value (Mean) and standard error (SEM). In all analyses differences with $p<0.05$ are determined as statistically significant. In normal distribution, the values are juxtaposed through Independent Samples T-test. Tables and figures are built with program package Microsoft Office 2013. Applications MS Word and MS Excel are used.

Aim:
The aim of the current study is to determine the dynamics in the values of serum testosterone and PSA during replacement therapy with testosterone propionate dosed 4 and 8 mg/kg body weight (BW)

Results:
The orchiectomy decreased significantly the levels of serum testosterone at the 15 days trial and insignificantly at the chronic one. The supplementation with testosterone propionate increased its levels with significance at the higher dose. An increase in the serum levels of testosterone was observed at the aged male rats too, a result from the application of its propionate salt. Significance was received at the chronic use of dose 8 mg/kg BW.

The results of the present study show that as at the orchiectomized , thus at the aged male rats the application of testosterone propionate for 15 days or 15 weeks does not change the level of PSA towards controls. Even more –in all tested animals its value is zero.

Discussion:
PSA is a serum glycoprotein, produced by the normal prostate. It is used as a tumor marker, because its increased levels directly correlate with the risk of prostate cancer. Value above 4 ng / ml is an indication for prostate biopsy. More recent studies show that there is a risk of cancer at a value between 2, 6 and 4 ng / ml too. This raises the question for eventually lower upper border of PSA. More than 60 years ago, Huggins and al. (1941) demonstrate that the decrease of the testosterone depots leads to regression of the prostate cancer. There are clinical cases described, which show that TRT can turn occult cancer into a clinically manifested one. Newer studies show low frequency of TRT associated prostate cancer. Lots of prospective studies over TRT establish only 5 cases of prostate cancer among 461 men, observed for 6 up to 36 months. The frequency established is similar to that in the common population.

When we look in the literature reviews we can see a lot of reports which show that there is no connection between the progression of prostate cancer and the application of testosterone. TRT in normal men and in those with increased risk of prostate cancer doesn't raise its frequency. Surprisingly, at a thorough prospective study is established increased risk of prostate cancer at low values of testosterone. Morgentaler and al. (2006) also prove development of prostate cancer in 11 from 17 hypogonadial men. When young men are concerned, the studies establish that the application of exogenic testosterone doesn't raise the levels of PSA and the prostate volume. The latest studies show that TRT has neither statistically significant effect over the levels of the total and the free PSA, nor over their correlation. The frequency of prostate cancer at long-term TRT is equivalent to that, expected in the common population.

Our results confirm the clinical data quoted above, about the safety of testosterone therapy towards prostate cancer. Nevertheless, a patients' monitoring is needed, because the frequency of the disease increases with the age. The current study is the first one, demonstrating the influence of testosterone propionate over the serum levels of PSA in experimental model of hypogonadism (orchiectomy, aged animals).

Conclusion:
Testosterone propionate, applied to rats with androgen deficiency at a dose of 8 mg/kg BW restores the physiological levels of the total testosterone and doesn't change the values of PSA.

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