



Research Articles

Effect of Testosterone Supplementation on Renal Function in Male Albino Rats

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SUMMARY

Objectives: Testosterone is an anabolic steroid and it is secreted primarily by the testicles in males. Androgens have been shown to increase tubular sodium and water reabsorption and activate various vasoconstrictor systems in the kidneys. Testosterone increases blood pressure and may also influence renal electrolyte excretion.

Methods: Fifteen adult male rats weighing 100 – 150g were randomly divided into three groups of five (5) rats each. Group 1 rats (Control) were given normal saline intramuscularly (IM). Group 2 rats were given 3mg/kg body weight (bw) of testosterone IM while Group 3 rats were given 9mg/kg bw testosterone IM for two weeks. All rats were allowed normal chow and water *ad libitum*. The animals were sacrificed under anaesthesia and blood samples collected through cardiac puncture.

Results: Plasma urea levels of both low ($2.02 \pm 0.23 \text{ mmol/L}$) and high ($10.3 \pm 0.61 \text{ mmol/L}$) dose testosterone-treated animals were higher when compared with the Control group ($1.94 \pm 0.07 \text{ mmol/L}$), but the difference was only significant ($p < 0.05$) in the high dose group. A significant ($p < 0.05$) increase in plasma creatinine level in animals injected with low dose testosterone ($33.0 \pm 2.46 \mu\text{mol/L}$) and high dose testosterone ($46.0 \pm 5.67 \mu\text{mol/L}$) was observed when compared to the control group ($25.2 \pm 3.91 \mu\text{mol/L}$).

Conclusion: It was concluded from this study that exogenous administration of testosterone may alter normal kidney functions shown by elevated levels of urea and creatinine, but these could also be dose-dependent.

INTRODUCTION

Testosterone is a steroid hormone from androgen groups and is found in mammals, reptiles [1], birds [2] and other vertebrates. In animal, it is secreted primarily by the testicles in males and in small amounts by the ovaries and adrenal glands in females. [3] It is the principal male sex hormone with anabolic activity.

In men, testosterone plays a key role in the development of male reproductive tissues as well as expression of sexual characteristics. [4] In women, it is required for hair growth distribution and clitoral enlargement. In addition, testosterone is essential for health and well-being, especially in prevention of osteoporosis in females. [5] On the average, in adult human males, the plasma concentration of testosterone is about 7 – 8 times as great as the plasma concentration in females. [6]

The original and primary use of synthetic testosterone is for the treatment of males with too little or no natural endogenous testosterone production (hypogonadism). Appropriate use for this purpose is legitimate hormone replacement therapy (HRT), which still maintains serum testosterone levels within the normal reference range. [7] The application of HRT using testosterone supplements in the elderly is on the increase. Testosterone is given in aging men and women to improve their sexual drive, [8] and in male to

also sustain the skeletal frame work and improve the general quality of life. [6,9] It is even popular and abused among professional sporting individuals.

Endocrine abnormalities are a common feature of chronic renal insufficiency. [10,11] The kidneys are essentially regulatory organs which maintain the volume and composition of body fluids through filtration of the blood, selective reabsorption and secretion of filtered solutes. Androgens have been shown to increase tubular sodium and water reabsorption and activate various vasoconstrictor systems in the kidneys, such as the renin-aldosterone-angiotensin system (RAAS), and endothelin. [12] Testosterone increases blood pressure and may also influence renal electrolyte excretion. [13]

Uncontrolled usage of testosterone derivatives may lead to serious side effects such as cardiovascular system disorders, lipid metabolism disorders or insulin sensitivity. [14,15] Androgens are a risk factor in the development of glomerulosclerotic injury. [14,15] In addition, when used as performance-enhancing agent, [16] it may cause ethical problems such as psychological and emotional problems often referred to as roid rage. [17] Creatinine and urea have been explored and have been incriminated as renal injury indicators, thus they are used in the assessment of renal function. [18]

The increased use of testosterone supplements in aging individuals has been popularized despite the fact that not much rigorous clinical trials have been explored in examining the effects of testosterone administration on the cardiovascular-renal disease risk.[19] This study was carried out to investigate the effect of acute administration of exogenous testosterone on renal function in male albino rats.

MATERIALS AND METHODS

Drug Preparation

Testosterone propionate is a fixed ester. It is commercially available as 25mg/dl in one ampoule of 2mls. Doses selected were 3mg/kg bw and 9mg/kg bw, for low dose and high dose administration, respectively.[20]

Animals and Drug Administration

Fifteen adult male rats weighing 100 – 150gm were used for this study. They were housed and bred in the animal house of the Faculty of Basic Medical Sciences, University of Ilorin. The experimental protocol was conducted in accordance with internationally-accepted principles for laboratory animal use and care. The animals were kept in standard metabolic cages with adequate ventilation and allowed access to feed and water ad libitum. The rats were randomly divided into three groups of five (5) rats each. Group 1 rats (Control) were given 0.1 ml normal saline intramuscularly (IM). Group 2 rats were given 3mg/kg bw of testosterone IM while Group 3 rats were given 9mg/kg bw of testosterone IM for two weeks.

Blood Sample Collection

At the end of the treatment period, the animals were sacrificed under ketamine anaesthesia and blood samples were collected through cardiac puncture following an anterior midline incision. The blood samples were collected into lithium heparin bottles for plasma electrolyte analysis.

Electrolyte Assay

Serum Sodium and Potassium analyses were performed with a Flame Photometer (Jenway Co. Ltd., Staffordshire, UK). It involves use of the frequency of light lost by free atoms of an alkali metal salt to characterize the alkali metal. Plasma Creatinine and urea were also assayed by a colorimetry method using a Spectrophotometer (Shanghai Mapada Instruments Co. Ltd, Shanghai City).

Statistical Analysis

All results were expressed as mean $\pm$ SEM. Data was analysed by one-way analysis of variance (ANOVA) and Duncan New Multiple Range Test (DMRT). Differences in mean were considered as significant at $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc. Released 2008. SPSS Statistics for Windows, Version 17.0. Chicago: SPSS Inc.).

RESULTS

The plasma urea levels of both low and high dose testosterone-treated animals were 2.02 ± 0.23 mmol/L and 10.3 ± 0.61 mmol/L, respectively; with a significant increase ($p < 0.05$) recorded only in the high dose-treated group when compared with the control group (1.94 ± 0.07 mmol/L). (Table 1). The animals in both experimental groups had significant

increases ($p < 0.05$) in plasma creatinine levels when compared to control. The plasma sodium and potassium levels in the low and high dose treated groups ($\text{Na}^+ 114 \pm 3.36$; $\text{K}^+ 55.0 \pm 3.53$ mmol/L and $\text{Na}^+ 115.0 \pm 2.81$; $\text{K}^+ 57.2 \pm 2.85$ mmol/L, respectively) were similar to ($p > 0.05$) those in the control group ($\text{Na}^+ 101.2 \pm 5.26$, $\text{K}^+ 54.2 \pm 2.81$ mmol/L).

Table 1: Effect of Testosterone on Serum Electrolyte, Urea and Creatinine Concentrations in Rats

Parameters	TESTOSTERONE		
	Control (distilled water)	Low dose (3mg/kg bw)	High dose (9mg/kg bw)
Sodium (mMol/L)	101.2 $\pm$ 5.26 mmol/L	114 $\pm$ 3.36 mmol/L	115.0 $\pm$ 2.81 mmol/L
Potassium (mMol/L)	54.2 $\pm$ 2.81 mmol/L	55.0 $\pm$ 3.53 mmol/L	57.2 $\pm$ 2.85 mmol/L
Urea (mMol/L)	1.94 $\pm$ 0.07 mmol/L	2.02 $\pm$ 0.23 mmol/L	10.3 $\pm$ 0.61 mmol/L*
Creatinine (mMol/L)	25.2 $\pm$ 3.91 μ mol/L	33.0 $\pm$ 2.46 μ mol/L*	46.0 $\pm$ 5.67 μ mol/L*

* $p < 0.05$ when compared to control; bw-body weight

DISCUSSION

Testosterone is a hormone that plays a vital role in sexual drive, growth, aging process, and overall health. It is commonly manipulated by athletes and aging adult in order to enhance their sport performance, improve their body composition and perhaps bring back their youthful virility.

Results showed an increase in plasma urea, which was significant only in the high dose testosterone treated rats. This is in tandem with the findings of Wu *et al.*[21] who reported an increase in plasma urea after evaluating the secondary impact of a prototype androgen contraceptive regimen on physical, metabolic and behavioural variables.

As the kidneys become impaired for any reason, the creatinine level in the blood will rise due to poor clearance of creatinine by the kidneys. Abnormally high levels of creatinine thus warn of possible malfunction or failure of the kidneys.[22] The significant increase in plasma creatinine level recorded in both treated groups suggested a degree of impairment in renal function. This agrees with the work of Park *et al.* [23] who suggested that testosterone is responsible for enhanced susceptibility of males to ischemic renal injury following elevated levels of creatinine in castrated mice treated with testosterone. However, Wu *et al.*[21] reported a decrease in plasma creatinine levels following a long-term administration of testosterone. Data from experimental studies support the hypothesis that exogenous administration of testosterone may induce the activation of the renin-angiotensin system (RAS), the production of endothelin and the regulation of anti-or/and proinflammatory cytokines involved in the pathogenesis of hypertension and kidney damage.[24] Also, testosterone either activates androgen receptors in its unchanged form or gets converted to 5 α -dihydrotestosterone by the enzyme 5 α -reductase and then binds to androgen receptors. Once bound, the receptors-hormone complex moves into the cell nucleus and binds to specific genes sequences on the cellular DNA. This leads to modification of proteins, thereby giving rise to the androgenic effects exerted by testosterone. It is known that cultured mesangial cells from male rats contain nuclear receptors for

testosterone.[25] In addition, it is believed that renal tubular cells contain nuclear receptors for testosterone,[26] which has been associated with tubular cells apoptosis. This may be a link to the mechanism for the derangement in renal function observed in this present study. Though, testosterone supplements taken orally or parenterally have been used to correct many clinical conditions, however, it has also been indiscriminately widely abused.[7]

CONCLUSION

We conclude that inappropriate exogenous administration of testosterone may alter normal kidney functions as seen by elevated levels of urea and creatinine, and although these could be dose-dependent, great caution should be taken when testosterone supplements are used, as it could predispose to abnormal renal functions that may consequently precipitate renal diseases.

Conflict of Interest

The authors declare no competing interests.

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