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Effect of Nandrolone Decanoate, Boldenone Undecylenate on Renal Status of Rabbits (*Oryctolagus cuniculus*)

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Abstract: The present study was designed to assess the effects of Nandrolone Decanoate (ND), Boldenone Undecylenate (BOL) and combination of both (ND+BOL) on renal system of male rabbits. Thirty five adult rabbits were divided into four groups. Group A served as control group and group B received 4.5mg/kg body wt ND, group C 10mg/kg body wt received BOL and group D 14.5 mg/kg body wt received ND+BOL. Rabbits were injected intramuscularly twice a week for a period of six weeks. ND, BOL and ND+BOL treatments had no significant effects on body weight. Whereas Urea, Creatinine, Total Protein, Albumin, Globulin, Bilirubin and Triglyceride concentrations had increased significantly ($p < 0.05$), While in contrast Cortisol concentration significantly ($p > 0.05$) decreased in treated groups compared to control group. It is concluded that administration of ND, BOL and ND+BOL exerts asignificant effect on the renal system of adult rabbits.

Key words: Steroids · Kidney · Urinary System · Athletes · Bodybuilders

INTRODUCTION

Anabolic androgenic steroids (AAS) are synthetic derivatives of the male testosterone hormone. These synthetic derivatives are used to increase weight, body mass, provide power to compete and for the betterment of physical appearance [1]. Hence prevalence of AAS is much higher among young men compared to general population. Sportsmen, athletes and body builders frequently use AAS to improve athletic performance [2, 3]. Over 60 different forms of AAS are easily available in market, that are prescribed to patients suffering from diseases like hypogonadism, cachexia associated with HIV, cancer, burns, renal and hepatic failure and anaemia associated with leukaemia [4,5]. However, irrespective of their medicinal use, illegal use of AAS has been tremendously increased over the last few decades into a widespread drug abuse and cosmetic purposes to enhance appearance both in developing and developed countries [6,7].

Boldenone (1-dehydro derivative of testosterone) has been banned due to its adverse effects on human body [8]. It is directly intake to build muscles and indirectlyby the intake of animal meat that is exposed to Boldenone. However little is known about the adverse effects on liver, renal system and testes structure of adolescent animals. Tousson *et al*. [9] documented Chronic renal injury may occur by the Boldenone Undecylenate, which may ultimately lead to a progressive renal failure. Whereas Nandrolone Decanoate (19-nortetosterone, 17-hydroxyest r-4en3-one) has both anabolic and androgenic activities [1,10]. It has significant effect on production of red blood cells and prolongs their survival [11] in addition to this, Nandrolone Decanoate has numerous adverse effects including acne, abnormal liver function, virilization, discomfort from intramuscular injection. Moreover it increase weight, triceps skinfold thickness, nitrogen balance, reduction of HDL cholesterol and it regularly cause an increase in LDL cholesterol and bone mineral density [12,13].

Keeping in view the above discussion, it is evident that little studies are available on the effects of anabolic steroids on renal system and other body organs of living organisms [9]. In this perspective, the present study was designed to assess the individual and combined effect of Nandrolone Decanoate and Boldenone Undecylenateon

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renal system of rabbit.For this purpose, biochemical changes in blood were evaluated to determine the associated adverse effects with level of toxicity on the basis of time exposure.

MATERIALS AND METHODS

The present study was conducted in animal house of Lahore College for Women University (LCWU), Lahore to determine the effects of Anabolic Androgenic Steroids on rabbits. Thirty five adult male rabbits *(Oryctolagus cuniculus)* were acclimatized for a week before the treatment. Rabits were kept in April 6, 2015 the same yard with natural light and temperature conditions, maintained by using room coolers. Green fodder, fresh fruits (e.g. watermelon), vegetables (cucumber, carrots, radish, beet root, spinach), corn and wheat were provided as food thrice a day and free access to fresh tap water. Body weight of each rabbit was measured prior to start of the experiment and then after each week of dose administration.

The rabbits were randomly assigned into four groups (one control group and three experimental groups). The control group (n=8) was treated with a vehicle. Sesame oil was administered twice a week up to 6 week treatment. While in experimental groups viz. B, C and D (n=9 in each group) AAS were administered with intramuscular injection of Nandrolone Decanoate, Boldenone Undecylenate and combination of both respectively. Group-B received ND 4.5mg/kg body weight, Group-Creceived BOL 10mg/kg body weight whereas group-D received ND+BOL 14.5mg/kg body weight [14].

The blood sample of each rabbit was collected at the end of each week by cleaning the puncture site with cotton swab dipped in alcohol. It allows the free flow of blood from ear lobe vein into labeled heparinized (3ml) syringes.The collected blood samples were shifted in tubes (marked with identity number) and later on centrifugation was made by using centrifuge machine (WiseSpin® CF-10) at 3500-4000rpm for 15 minutes.Plasma was separated from blood clot by using pasture pipette in marked eppendorfs and stored below -10°C for further analysis.

The biochemical parameters viz. renal function tests (blood urea, serum Creatinine), Total Protein, Albumin, Globulin, Bilirubin, Triglycerides and Cortisol were evaluated by using automated biochemistry chemistry analyzer (URIT-800)in the biochemistry laboratory Lahore College for Women University (LCWU), Lahore.

Statistical Analysis: The obtained data was analyzed by One-way ANOVA by using SPSS (Version 13). P-value of 0.05 was considered as significant in statistical analysis. The result was expressed as mean ± standard error (SEM).

RESULTS

Body Weight: The rabbits treated with Nandrolone Decanoate (ND), Boldenone Undecylenate (BOL) and combination of both (ND+BOL) showed gradual increase in their body weight with time, the maximum increase 1.47±0.03, 1.51±0.09 and 1.58±0.09 kg were recorded in the sixth week of the treatment in ND, BOL and ND+BOL respectively over the control group (1.40±0.03 kg). While ND (1.26±0.02 kg) and ND+BOL (1.27±0.04) treated group indicated slight decrease in third week and BOL (1.30±0.03 kg) during the fourth week of treatment (Table 1). However overall all treated groups had non-significant ($p > 0.05$) difference compared to control group(Table 2).

Urea and Creatinine: Rapid increase in urea concentration was recorded in the first and second week of treatment and this increase remained consistent throughout the study in all treated groups compared to control group. Similar trends were recorded for the concentration of Creatinine, however Creatinine showed unusual decrease during third (2.99 ± 0.21 mg/dl) and forth (2.41 ± 0.16 mg/dl) weeks, when treated with ND and ND+BOL respectively. The sixth week showed maximum increase in urea concentration with all treatments and similar trend was found for Creatinine concentrations. The combined effects of ND+BOL was found higher than the individual dosage of ND and BOL except during the sixth week, while creatinine concentration was much higher in ND+BOL treated group throughout the experiment (Table 1). Moreover both urea and creatinine concentrations were significantly ($p < 0.05$) different among all treated and control groups (Table2).

Total Protein: Total protein concentration had significant ($p < 0.05$) difference in all treated and control group (Table 2) however temporal fluctuations were found among all four groups. The maximum concentration was recorded during the sixth week in all treated groups. These treated groups showed rapid increase in total protein concentration during the first week, however concentration decreased during the second, third and forth weeks compared to first week, except ND and ND+BOL treated groups during third and forth weeks respectively. Moreover ND+BOL had maximum value compared to ND and BOL treated groups (Table 1).

Table 1: Fluctuation in Body weight, Urea, Creatinine, TP, Albumin, Globulin, Bilirubin, TG and Cortisol of male Rabbits during 1st, 2nd, 3rd, 4th, 5th and 6th week of ND, BOL and ND+BOL treatments.

		Time in Weeks					
Parameters	Treatment	1st	2nd	3rd	4th	5th	6th
Body weight (kg)	Control	1.19±0.03[a]	1.22±0.09[c]	1.26±0.02[b]	1.31±0.02[a]	1.36±0.02[c]	1.40±0.03[d]
	ND	1.15±0.02[b]	1.27±0.06[b]	1.26±0.02[b]	1.31±0.02[a]	1.38±0.03[b]	1.47±0.03[c]
	BOL	1.14±0.03[b]	1.20±0.02[d]	1.31±0.06[a]	1.30±0.03[a]	1.39±0.03[b]	1.51±0.09[b]
	ND+BOL	1.14±0.05[b]	1.30±0.02[a]	1.27±0.04[b]	1.30±0.07[a]	1.43±0.06[a]	1.58±0.09[a]
Urea (mg/dl)	Control	28.43±1.23[d]	29.62 ± 1.94[c]	26.44 ± 3.13[d]	22.76 ± 3.46[d]	20.26 ± 2.71[d]	25.48 ± 2.11[d]
	ND	32.75 ± 1.30[c]	38.19 ± 1.92[a]	41.23 ± 1.99[c]	42.98 ± 0.84[c]	43.83 ± 1.23[b]	48.09 ± 1.62[a]
	BOL	33.07 ± 630[b]	35.21 ± 1.69[b]	32.48 ± 3.10[b]	41.81 ± 1.30[b]	44.20 ± 3.50[a]	45.07 ± 1.16[c]
	ND+BOL	33.33 ± 3.03[a]	38.19 ± 2.15[a]	42.38 ± 0.74[a]	44.86 ± 2.31[a]	41.21 ± 2.82[c]	47.95 ± 2.21[b]
Creatinine (mg/dl)	Control	1.91 ± 0.20[d]	1.96 ± 0.14[d]	1.40 ± 0.23[d]	1.45 ± 0.22[d]	1.64 ± 0.22[d]	2.08 ± 0.09[d]
	ND	2.12 ± 0.19[c]	2.47 ± 0.33[b]	2.49 ± 0.18[c]	2.41 ± 0.16[c]	3.04 ± 0.23[c]	3.59 ± 0.16[c]
	BOL	2.23 ± 0.36[b]	2.38 ± 0.27[c]	2.59 ± 0.14[b]	3.01 ± 0.37[b]	3.41 ± 0.25[b]	4.09 ± 0.37[b]
	ND+BOL	2.71 ± 0.16[a]	3.14 ± 0.27[a]	2.99 ± 0.21[a]	3.61 ± 0.30[a]	4.26 ± 0.20[a]	4.26 ± 0.35[a]
TP (g/dl)	Control	6.81 ± 0.43[d]	6.75 ± 0.41[d]	6.28 ± 0.31[d]	6.32 ± 0.15[d]	7.22 ± 0.25[d]	6.95 ± 0.29[d]
	ND	7.33 ± 0.27[c]	7.20 ± 0.22[b]	7.54 ± 0.22[b]	7.17 ±0.41[c]	8.56 ± 0.29[b]	9.76 ± 0.37[c]
	BOL	7.99 ± 0.66[a]	6.91 ± 0.54[c]	7.16 ± 0.33[c]	7.32 ± 0.24[b]	8.43 ± 0.31[c]	9.85 ± 0.21[b]
	ND+BOL	7.80 ± 0.21[b]	7.58 ± 0.42[a]	8.45 ± 0.56[a]	9.02 ± 0.34[a]	9.21 ± 0.47[a]	10.92 ± 0.19[a]
Albumin (g/dl)	Control	3.75 ± 0.41[d]	3.56 ± 0.23[d]	3.73 ± 0.15[d]	3.52 ± 0.16[d]	3.72 ± 0.15[d]	3.75 ± 0.36[d]
	ND	3.77 ± 0.21[c]	3.89 ± 0.06[c]	4.01 ± 0.13[c]	4.13 ± 0.25[c]	4.26 ± 0.12[c]	4.40 ± 0.32[c]
	BOL	4.76 ± 0.34[a]	4.07 ± 0.34[b]	4.22 ± 0.35[b]	4.47 ± 0.34[a]	4.94 ± 0.48[a]	4.82 ± 0.51[b]
	ND+BOL	3.89 ± 0.25[b]	4.11 ± 0.21[a]	4.26 ± 0.22[a]	4.37 ± 0.31[b]	4.62 ± 0.41[b]	4.89 ± 0.44[a]
Globulin (g/dl)	Control	3.06±0.48[d]	3.19±0.47[d]	2.54±0.30[d]	2.80 ±0.25[d]	3.10 ±0.26[d]	3.20 ±0.41[d]
	ND	4.54± 0.18[b]	4.72± 0.29[b]	4.86± 0.21[c]	5.55± 0.18[b]	5.38± 0.24[b]	5.78± 0.30[a]
	BOL	3.73± 0.43[c]	4.81± 0.35[a]	5.22± 0.43[b]	5.22± 0.33[c]	4.90± 0.57[c]	5.52± 0.49[b]
	ND+BOL	5.25±0.42[a]	4.37±0.15[c]	5.81±0.45[a]	6.18±0.06[a]	6.18±0.42[a]	4.89±0.34[c]
Bilirubin	Control	0.19 ± 0.09[d]	0.21 ± 0.02[c]	0.26 ± 0.09[d]	0.26 ± 0.02[c]	0.26 ± 0.06[d]	0.26 ± 0.06[d]
	ND	0.71 ± 0.06[c]	0.72 ± 0.05[b]	0.73 ± 0.08[c]	0.87 ± 0.04[b]	1.14 ± 0.17[b]	1.16 ± 0.19[b]
	BOL	0.78 ± 0.04[b]	0.72 ± 0.04[b]	0.85 ± 0.06[b]	0.89 ± 0.03[a]	1.12 ± 0.13[c]	1.02 ± 0.06[c]
	ND+BOL	0.82 ± 0.02[a]	0.85 ± 0.03[a]	0.90 ± 0.06[a]	0.89 ± 0.04[a]	1.19 ± 0.14[a]	1.20 ± 0.08[a]
TG (mg/dl)	Control	19.31[d]	18.26[d]	11.22[d]	21.26[d]	4.14[d]	5.29[d]
	ND	120.60 ± 15.61[c]	153.25 ± 26.77[c]	157.55 ± 12.57[c]	185.84 ± 6.72[b]	179.30 ± 12.76[a]	177.91 ± 29.70[c]
	BOL	164.79 ± 34.36[a]	158.49 ± 12.37[b]	164.05 ± 16.55[b]	167.70 ± 17.90[c]	177.68 ± 20.45[b]	192.51 ± 16.39[b]
	ND+BOL	159.51 ± 11.22[b]	158.81 ± 13.58[a]	166.04 ± 18.17[a]	186.52 ± 8.46[a]	175.22 ± 16.49[c]	203.55 ± 11.04[a]
Cortisol (nmol/l)	Control	88.53 ± 5.11[a]	86.05 ± 4.82[a]	82.63 ± 3.70[b]	83.57 ± 2.65[b]	85.02 ± 5.04[a]	80.93 ± 2.76[a]
	ND	70.41 ± 4.81[b]	67.91 ± 3.60[c]	65.68 ± 3.47[c]	69.68 ± 3.76[c]	68.27 ± 2.66[d]	66.19 ± 3.52[d]
	BOL	66.65 ± 5.70[c]	69.66 ± 5.22[b]	84.98 ± 6.20[a]	85.99 ± 6.83[a]	74.39 ± 5.28[b]	70.61 ± 5.08[b]
	ND+BOL	52.93 ± 2.41[d]	57.27 ± 3.02[d]	47.09 ± 4.63[d]	60 ± 4.30[d]	70.88 ± 4.44[c]	69.61 ± 2.0[c]

*Means with different superscripts a, b, c, d within coloumn of each parameter are significantly different at $p< 0.05$

*ND: Nandrolone Decanoate, BOL: Boldenone Undecylenate

Table 2: Effect of ND, BOL and ND+BOL treatments on Body weight, Urea, Creatinine, TP, Albumin, Globulin, Bilirubin, TG and Cortisol of male Rabbits.

	Control Groups		Treated Groups			
Parameters	Mean ± SE	Mean ± SE (ND)	Mean ± SE (BOL)	Mean ± SE (ND+BOL)	F-value	p-value
Body weight	1.29±0.033[a]	1.30±0.044[a]	1.30±0.054[a]	1.33±0.061[a]	0.35	0.788
Urea (mg/dl)	25.49±1.430[d]	41.17±2.144[b]	38.64±2.331[c]	41.32±2.09[a]	813	<0.001
Creatinine (mg/dl)	1.74±0.115[d]	2.68±0.217[c]	2.95±0.287[b]	3.49±0.269[a]	189	<0.001
TP (g/dl)	6.72±0.148[c]	7.92±0.423[b]	7.94±0.445[b]	8.83±0.493[a]	900	<0.001
Albumin (g/dl)	3.67±0.042[d]	4.07±0.095[c]	4.54±0.143[a]	4.35±0.146[b]	312	<0.001
Globulin (g/dl)	2.98±0.106[d]	5.13±0.204[b]	4.9±0.256[c]	5.44±0.300[a]	143	<0.001
Bilirubin	0.24±0.012[c]	0.88±0.086[b]	0.89±0.061[b]	0.97±0.070[a]	287	<0.001
TG (mg/dl)	77.97±2.77[c]	162.40±9.882[b]	170.8±5.03[a]	1.74±7.14[d]	350	<0.001
Cortisol (nmol/l)	84.45±1.095[a]	68.02±0.760[c]	75.38±3.35[b]	59.63±3.80[d]	372	<0.001

*Means with different superscripts a, b, c, d within row are significantly different at $p< 0.05$

*ND: Nandrolone Decanoate, BOL: Boldenone Undecylenate

Albumin: The ND treated group showed gradual increase in the albumin concentration from first (3.77 ± 0.21 g/dl) to the last week (4.40 ± 0.32 g/dl) of treatment compared to control. While BOL and ND+BOL treated groups during first week showed increase (4.76 ± 0.34 g/dl and 3.89 ± 0.25 g/dl) in albumin concentrations respectively compared to control and decreased during the second, third, fourth and fifth weeks except BOL treated group during fifth week compared to first week. Moreover ND+BOL treated group had maximum concentration throughout experiment compared to individual values, except fourth and fifth weeks had slightly less concentration compared to BOL treated group (Table 1). Overall there was significant ($p < 0.05$) difference among studied groups (Table 2).

Globulin: Globulin concentration was found maximum in fourth and fifth weeks (6.18±0.06 g/dl) in the combined dosage group compared to control and other treated groups. Moreover during first week this treatment rapid and maximum increase was recorded, while this trend goes downward during second (4.37±0.15 g/dl) and sixth week (4.89±0.34 g/dl) of treatment. This trend of globulin increase was also found with ND and BOL treated groups compared to control group, whereas during fifth week showed slight decrease in concentration (Table 1).

Bilirubin: Bilirubin concentration was found significantly higher in all treated groups compared to control group throughout the experiment and it gradually increased with time. The maximum level of Bilirubin was recorded in the fifth and sixth week of treatment in all treated groups. Maximum increase was observed in fifth week of treatment in all treated groups. Whereas sixth week treatment showed slight decrease in bilirubin level compared fifth week. BOL+ ND treatment had maximum increase in all weeks of treatment (Table 1). Overall there was significant ($p < 0.05$) difference in the concentration of bilirubin among all treated and control group (Table 2).

Triglycerides: Triglycerides concentration was recorded much higher in all the treated groups compared to control group throughout the experiment. However ND+BOL treated group had maximum concentration TG during third, fourth and sixth week of treatment compared to ND, BOL (Table 1). Overall there was a significant ($p < 0.05$) difference among studied groups (Table 2).

Cortisol: Cortisol level decreased significantly ($p < 0.05$) in ND, BOL and ND+BOL treated groups compared to control group (Table 2). Maximum decrease in cortisol level was recorded with the treatment of ND+BOL throughout the experiment, however little rise in cortisol was found during the fifth and sixth week, followed by ND and BOL treated groups compared to control group (Table 1).

DISCUSSION

The present study was performed to evaluate the effects of ND, BOL and combination of both ND and BOL on body weight, urea, creatinine, total protein, albumin, globulin, bilirubin and cortisol in male rabbits. Our study revealed that treatment with ND, BOL and ND+BOL had no significant effect on body weight in male rabbits. Similar results have been documented by Karbalay-Doust and Noorafshan [18] with ND treatment. Tahtamouni *et al*. [19] found non-significant increase in rats body weight with the administration of AAS. However Carson *et al*. [20] documented effects of AAS on body weight is controversial.

The increase in urea concentration with treatment of AAS is attributed to severe reduction in kidney function [13]. Such as Nephrosclerosis and disruptive glomerulosclerosis has been observed in AAS users e.g. rats [21] and acute renal failure in clinical patients (bodybuilders), which in turn is responsible for fluid and electrolyte imbalance [22,23]. The present study indicated significant increase in urea concentration treated with ND, BOL and ND+BOL. These results are consistent with the previous findings of reference [12,13]. This increase might be due to high level of urea concentration in serum,which is affected by high level of uric acid and hyperphosphatemia [24]. Anabolic steroids have mineralocorticoid effect and diuretics combines with the steroids lead to mask their effects. Moreover AAS are responsible for increase in muscle bulk and consequently creatinine level rise in the body [25]. SimilarilyTaher *et al*. [24] reported significantly higher serum creatinine concentrations in AAS user athletes.

The present study revealed that total protein, albumin and globulin were significantly higher in ND, BOL and ND+BOL treated groups compared to control group, furthermore it is noted that combined treatment of ND+BOL enhanced the individual effects of both ND and BOL. Griggs *et al*. [26] and Gabr *et al*. [27] has found

similar results with 2.5mg and 5mg BOL treatment. This increase in total protein concentration might be the result of the binding of BOL to androgen receptors at the cellular level, which in turn stimulate the production of RNA and consequently increase in protein formation [28]. AAS not only increase the protein synthesis in muscles, but also stimulate the production of circulating proteins [29,30]. BOL treatment has same effects on albumin concentration [27]. Albumin in blood regulates the flow of water between tissue fluid and plasma by affecting the colloidal osmotic pressure [32]. Whereas increase in globulin level with BOL treatment has been empirically proved [27]. This increase might be due to antibody secretion in case of any infection [32] or due to the retention of larger non-albumin proteins in the damaged glomerulus and in hypoalbuminemia conditions [33]. Moreover the ND+BOL treated group showed hyperglobuliminemia, which might be due to improved antibody secretion in infection or illness. However hyperglobulinemia in the present study can be explained due to the mutual effect of both steroids [34,35].

Hyperbilirubinemia observed in treated groups reflects the coexistence of established risk factors for kidney damage due to decreased glomerular filtration rate [36]. However slightly less concentration of bilirubin in BOL treated groupduring sixth week might be due to Bilirubin concentration fluctuation linked with AAS use. Plea [37] reported that androgens can selectively interfere with bile excretion by the liver enlightening the formation of canalicular bile plugs. Washington and Van Hoosier [30] found that Bilirubin is released in rabbits in monoconjugated form rather than diconjugated form which occur in most species.

The increase in serum triglyceride in present study is positively correlated with the intake of AAS. Taher *et al*. [24] reported 40-50% serum triglycerides increase in bodybuilders and other power-training athletes along with the decrease in serum HDL-C. Whereas, ND+BOL treatment synchronized the individual effects of steroids used in the present study. These results are in line with the findings of Alen *et al*. [38].

Significant decreased in cortisol level indicates the presence of androgen receptors in kidney, moreover AAS is responsible for the decline of hormone-binding proteins in the circulatory system [41, 42]. However increase in cortisol level with BOL treatment might be due to the type of AAS used or duration study [43]. Based upon competitive experiments, it is postulated that interaction of androgens with glucocorticoid receptors prevents the binding of glucocorticoids and might be responsible for the anabolic effects of pharmacologic doses of androgens in muscle [44].

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