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Hormonal and Histomorphological impacts of Oral Mesterolone (Proviron) in Adult Male Sprague Dawley Rats' Epididymes.

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***Abstract**: Concern has been expressed worldwide about Anabolic-androgenic steroids (AAS), one of the most widely abused drugs by athletes and muscle builders with gain to improving their performance and muscle mass in recent times. Moreover, AAS offer inappreciable benefits to infertile and sub-fertile males, with possible deleterious effects on both human and animal physiology including sperm quality. Due to the paucity of knowledge, the present study aimed to evaluate Mesterolone (AAS) impacts on adult male Sprague-Dawley rats' epididymes using serum hormones and histomorphologic assessment. Twenty adult male Sprague Dawley rats divided into two groups of 10 each. The treated group received 0.06mg/ g body weight/ day of Mesterolone (Proviron) by oral gavage for forty-two days while the control group received the equal volume of 0.9% normal saline per day. SPSS analysis of data generated with $P< 0.05$ considered statistically significant. The result showed lower significant ($P< 0.05$) body weight gain in the Proviron group. However, the raw epididymal weight and relative epididymal weight per 100g bwt were both higher significantly ($P< 0.05$) in the Proviron-treated than the control groups. Where as, T and FSH were significantly ($P< 0.05$) lowered in Proviron group than the control. Evidence of regressive changes with irregularly shaped tubules, tubular lumen dilatation, reduced epithelial height and basement were observed in the epididymes of Proviron-treated animals. Thus, Mesterolone usage has undesirable effects on the epididymes and short, intermittent therapy is advice for desirable outcomes.*
Key words: *Proviron; AAS; Histology; Morphology; Hormonal assay; SD rats; Epididymis*

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I. Introduction

Anabolic-androgenic steroid (AAS) is one of the most widely abused drugs in sports by athletes and muscle builders with the sole purposes of improving performance, ability, appearance or building muscle mass [1,2]. However, increasing concern about AAS is expressed recently because of its inappreciable benefits to infertile and sub-fertile males; and its possible deleterious effects on both human and animal physiology including sperm quality [1, 2]. Moreover, data from the Canadian Centre for Drug-Free Sport in 1993 also estimated that about 83,000 children in adolescent schools between the ages of 11-18 had used AAS in the preceding one year [1,3] and this is bound to be on the increase [1].

AAS consists mainly of endogenous testosterone –T (natural) and their exogenous synthetic derivatives. Which are produced or modified for enhanced anabolic activities and uses such as, to stimulate appetite and muscle growth, treating chronic wasting conditions (in cancers, AIDS, etc.), inducing male puberty, promoting protein synthesis and muscle growth [4,5]. Besides, over 100 synthetic T-derivatives are available in the market today with different physiological impacts on the body, which includes anabolic effects on specific organs (for example, the muscles, bones, the heart, and kidneys) with a little 5α-reductase activity. Also, AAS mechanisms of actions are to displace glucocorticoids from their glucocorticoid receptors and inhibit muscle protein catabolism, thereby leading to overall anabolic or muscle building effect. Other direct and indirect anabolic impacts of AAS include increases in the creatine phosphokinase activity in skeletal muscle and increases in both circulating insulin-like growth factor (IGF)–1[5] as well as up-regulation of IGF-1 receptors

[4]. Moreover, the activity of AAS, especially testosterone induces protein synthesis, muscle fiber development, erythropoiesis, and stimulation of bone growth [4, 5, 7-9].

Furthermore, synthetic androgens are used for the treatment of male infertility or sub-fertility, based on the fact that spermatogenesis as a process is both androgenic and follicle stimulating hormone (FSH) – dependent [10-12]. Hence, androgenic stimulation helps to maintain both spermatogenesis and secondary sexual characteristics, especially in the male. The principal androgen in the circulation of men and adult males of most mammalian species including the rat after extensive literature search is testosterone (T), produced by Leydig cells of the testis [10, 13, 14]. Thus, the androgenic activity can either be through a direct stimulatory increase in intratesticular testosterone level, which in turn enhances spermatogenesis; and positively influences sperm transport and maturation through its action on epididymis, ductus deferens and seminal vesicles [15]. Or a rebound effect through the suppression of both spermatogenesis and gonadotrophins (FSH and luteinizing hormone-LH) secretion [1,2,14,15].

The epididymis is a steroid-dependent organ for sperm storage and allows for further physiological maturation (capacitation) and acquisition of fertilizing ability by the matured epididymal spermatozoa [12, 16]. The epididymal secretory products within its microenvironment are rich in anti-oxidant enzymes such as sialic acid, acetyl carnitine, glyceryl-phosphoryl choline (GPC), etc. They maintain the basic osmolarity of the epididymal luminal fluid [17]; a steroid-regulated process [18] necessary for stabilizing spermatozoal membranes [13,19,20]. Also, about 96% of the secreted testicular fluid is reabsorbed by the non-ciliated cells within the efferent ductules [21]. Furthermore, maintaining homeostasis at this level of the epididymis helps prevent the sperm from being over diluted and incapable of maturation within the epididymis. As such, any blockage or interference in the normal functioning of the estrogen receptors or estrogens may result in infertility [11,12, 22].

The anabolic and androgenic activities of AAS originate from their binding to and activation of the androgenic receptors (AR). Though, the difference in both biological actions will depend primarily on the organs and target tissues involved.

Furthermore, DHT androgenic activity is more potent than that of testosterone, through its amplifying effect on the T- activity to as much as 10-folds. Since DHT has a higher relative binding affinity for the receptor and forms a more stable complex with the AR that is not easily dissociable, thereby giving DHT a higher molar potency [23, 24]. Again, DHT is also formed from the irreversible conversion of testosterone by the action of 5α-reductase enzymes, whose activity is vital in the testicles, skin, prostate, intestines, brain, bones, and adipose tissues, etc. [25, 26]. Therefore, androgenic effects of AAS predominate in these organs [4, 27].

No doubt, DHT will indeed have beneficial effects on keeping one's estrogen in check; hence the reason for its abuse by sports machines. For example, with Proviron, the athlete obtains more muscle hardness since the androgen level increased and the estrogen concentration remains low. This impact is usually appreciated to be positively enhanced when taken with diet during the preparation for a competition. Oral AAS is well absorbed from the gastrointestinal tract and later undergoes biotransformation during the first-pass metabolism in the liver with some metabolites partly excreted through the bile into the feces [14]. However, female athletes with naturally a higher estrogen level than their male counterparts often take oral Proviron (AAS) as their steroid supplement, resulting in increased muscle hardness [4, 5].

Hence, due to the paucity of knowledge and the conflicting reports of AAS especially DHT analogue usage in clinical settings, we aim to evaluate the impact of oral Proviron (Mesterolone) on the adult male Sprague-Dawley rats' epididymes using hormonal and histomorphometric assessment tools.

II. Materials And Methods

Source of Drug

The oral Proviron used for this study was bought from Agege pharmaceuticals in Agege. Proviron SCHERING (PTY) LTD is a product of Schering AG Germany/Allemagne, LOT # WEA6WX, manufactured date (MFD): 06, 04, expiry date (EXP): 06, 2009. Each oral tablet contains 25mg of Proviron (Mesterolone - 17beta-hydroxy-1alpha-methyl-5alpha-androstan-3-one) with 20 tablets in a bottle and the preservatives methylparaben (0,02%) and propylparaben (0,01%).

Preparation of Drug

Proviron was dissolved in 100mls of distilled water to make up to 0.06mg/kg bwt/day, based on the physiological calculation for a 70kg man.

Animal

Twenty mature and healthy adult male Sprague Dawley rats weighing 120 to 200g were procured from animal house of Lagos State University, College of Medicine, Lagos and housed in well ventilated wire-wooden cages in the departmental animal house. They were maintained under controlled light schedule (12 hours Light:

12 hours Dark) at room temperature (28oC) and with constant humidity (40-50%). The animals acclimatized for seven days before the start of treatment. During this period, they were fed with standard rat chows/pellets supplied by Pfizer Nigeria Ltd and water ad-libitum. Ear tag applied for individual identification of the entire group animals.

Experimental Procedure

The rats were all randomly divided into two groups of ten rats each. Treated groups received 0.06mg/kg body weight /day of Proviron solution via gastric gavage (orogastric intubation) daily. The control group also received the equal volume of 0.9% (w/v) normal saline daily for six weeks.

For the present study, all procedures involving animals conformed to the guiding principles for research involving animals as recommended by the Declaration of Helsinki and the Guiding Principles in the Care and Use of Animals [28] and approved by the Departmental Committee on the ethics and research [2].

Animal Sacrifice

The rats were anesthetized after post overnight fasting using the procedure described in our previous study [12,16]. Also, weekly weighing of the animals carried out throughout the experimental period and before the sacrifice.

Organ Harvest

The whole epididymes were dissected out via a midline abdominal incision, then cleared of surrounding fats and blotted dry. The weights of the organ were measured using a sensitive digital balance and volume measured by water displacement using a 10ml measuring cylinder. Later, the sizes (length and width) were recorded by use of a sliding gauge (d= 0.1) before eventually fixed in freshly prepared 10% formol saline solution as described earlier in Shittu [11, 12]. The two epididymes harvested from each rat were measured, and their average value regarded as one observation.

Tissue Processing for Light Microscopy

Serial paraffin sections of 5 µm were obtained from fixed, processed epididymal tissues blocks and stained with H & E stains as prepared and previously described in our earlier study [11,16].

Hormonal Assay

The estimation of serum Testosterone and FSH were carried out using the procedure enclosed with the specific commercial kit purchased from Amersham International Plc. (Bucking- Hamshire, United Kingdom) as previously described in our study [11, 29].

Statistical analysis

The weight data were expressed in Mean + S.D while the other data were expressed as Mean ± S.E.M. Comparison between groups was done using the student t-test and non-parametric Mann-Whitney U test as the case may be. All the data were input into SPSS 12 software Microsoft computer (SPSS, Chicago, Illinois). Statistical significance was considered at $P \leq 0.05$ [29].

III. Results

The final mean average raw body weight gained by animals in control group-B is higher than the Proviron-treated group A. However, the study has shown that there is no significant difference between the control and Proviron-treated animal weight using ANOVA as reflected in table 1.

Also, both the raw epididymal weight (wt) and the relative epididymo-somatic weight (wt/100gbwt) of the Proviron-treated animals were significantly ($P < 0.05$) higher when compared to the control as shown in table 1 and figure 1.

The macroscopic examination of the Proviron treated animals' epididymes revealed whitish coiled fibrous tissues with each dimension measuring about 6 X 0.6 X 0.2 cm (0.72cm^3). While, in the control animals' epididymes showed a pink, fibrous coiled tissue with each dimension measuring about 6.2 X 0.5X 0.1 cm (0.31cm^3).

The light microscopic studies of the Proviron-treated epididymes showed evidence of atrophic numerous round and regressive epididymal structural changes with a fewer spermatozoa within the tubules as compared to control. Also, seen is evidence of narrowing of the basement with the reduction in the epithelial heights of the tubules and widening of the interstitium; and abundant fluid filled spaces. However, a few tubules still showed normal morphology in the Proviron-treated animals as seen on light micrographs at X100 magnifications, as also reflected in the Fig. 2.

Furthermore, the control group- epididymes contained numerous and regularly shaped tubules with abundant spermatozoa. In addition, stereocilia with tall ciliated columnar epithelium were found in the control group on light microscopic examination at X100 magnification, as also reflected in the Fig. 3.

The respective serum hormonal assays showed that the T and FSH levels in the Proviron group A were about 2.7 folds and 3.7 folds significantly ($P<0.05$) lower than the Control group B respectively, as reflected in table 2 and figure 2.

IV. Discussion

The rat, unlike the mouse model, is used in the present study based on its suitability for studying the impact of androgenic hormones within the male reproductive system; and because it operates on a two-way androgen model (DHT and T) for its sexual differentiation. [26, 30, 31]. Besides, a morphometric study using light microscopy is best evaluated as in the present study when the studied organ has attained a sizable dimension [1, 2, 32]. The weight gain in the control animals was not significantly different from that of the Proviron treated animals.

However, there were significant ($P<0.05$) epididymal growths (raw weights and relative epididymo-somatic weights) observed in the Proviron group-A as compared to the Control group B. This may be a result of water retention and decreased high-density lipoprotein (HDL) among its others impact in the body [27, 33, 34]. Again, the differential epididymal weights observed also correlated well with the epididymal dimensions measured in the present study, in which the proviron to control epididymal dimensional ratio was 2:1 (0.72cm3: 0.31cm3).

The significant low T and FSH levels observed respectively in the Proviron-treated group in table 2; may be responsible for fewer releases of spermatozoa from the testis into the epididymal tubular lumens for sperm maturation activities when compared to the Control group, as reflected in figure 3-4. Similarly, T ester (AAS) administration to man was found to cause a rapid suppression in gonadotrophins levels (FSH and LH) followed by the parallel decline in inhibin B and sperm concentration in a particular study [35]. Thus, it is possible that the proviron –AAS administration on the hypothalamo-pituitary-gonadal (HPG) -axis of the animals may be inhibin-related as observed in previous studies [1, 2]. Also, this may have accounted for the significant low FSH seen in the present study.

However, DHT has the tendency to amplify the effects of T on the male reproductive cells accounting for some of the residual spermatogenetic activities taking place within some seminiferous tubules leading to sperm maturation activities seen within some of the epididymal lumens in the present study.

Moreover, DHT analogue (AAS) administration is found to induce both morphological and cytological changes in rats. Such as, evidence of abnormal fluid accumulation (edema) within the tubular lumen and interstitia of the epididymes with associated abnormal widening of the interstitial spaces and relative epididymal weight gain as observed in the light of the present study.

In addition, there have been conflicting reports on the reversibility of the negative impact of AAS administration in adult men following withdrawal or discontinuity of the AAS. Similarly, further study need to be carried out on its possible roles as a male contraceptive as a result of its impact on the epididymis in the light of the present study.

V. Conclusion

It is therefore emphasized that the role of Proviron in the management of male infertility needs to be reviewed based on its undesirable impact on the epididymes in the present study. Again, caution must be applied in its usage by sports machines.

Moreover, the real battle here and way forward is educating our youths, non-athletes and athletes alike about the danger of AAS therapy or other performance enhancers and to refocus their energy on taking of adequate good diets coupled with proper training for sustainable and enhanced performance as desired.

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Table 1. Summary of Body Weights And Organ Weights Of Animals

ANIMAL GROUP	Pre-experimental weight (g) (Mean + S.D)	Final body weight(g) (Mean + S.D)	Raw Epididymal weight (g) (Mean + S.E.M)	Epididymo-somatic body weight (wt/100gbwt) (Mean + S.E.M)
Proviron (n=10)	159.4 + 5.16	185.2 + 12.80*	0.70 + 0.02*	0.39 + 0.01*
Control (n=10)	127.3 + 6.40	184.4 + 12.60	0.55 + 0.03	0.30 + 0.02

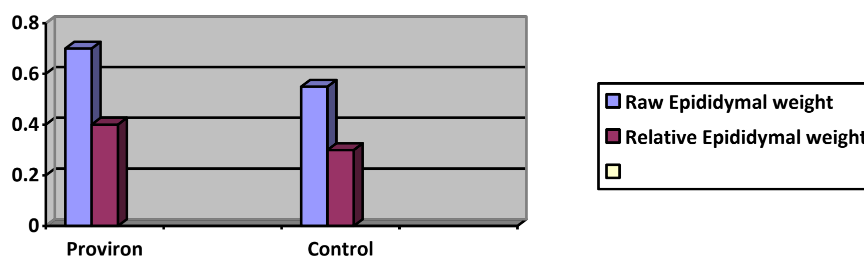
n = number of rats per group.
Values are mean ± SEM (in-vitro weighing) and mean ± S.D (in-vivo weighing)
*: Significantly different from the control group at <0.05.

Table 2. Summary Of Hormonal Profiles Of The Animals

Animal Group	Testosterone-T (ng/ml)	FSH (I.U)
Proviron (n =10)	0.30 + 0.10*	3.0 + 0.40*
Control (n = 10)	0.80 + 0.03	11. 0 + 2.30

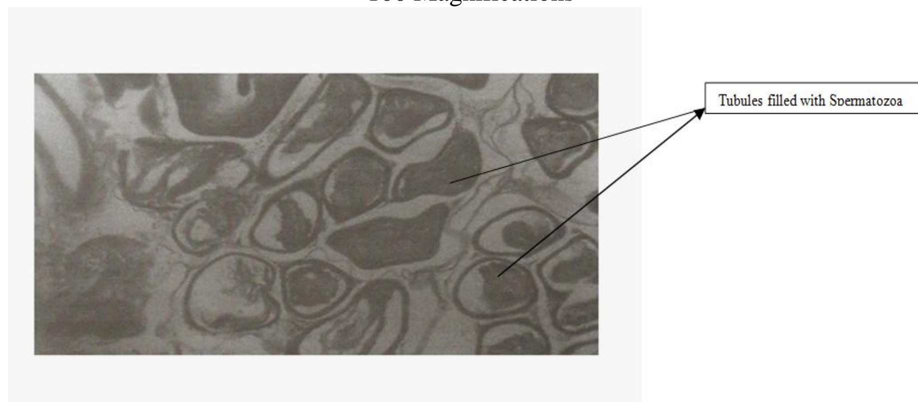
n = number of rats per group,
Values are mean ± SEM,
*: Significantly different from the control group at <0.05.

Figure 1. Comparison Of Raw Weight And Relative Weight Of The Epididymes (Wt/100g Body Wt) In Both Groups



Both the raw epididymal weight and the relative epididymo-somatic weight of the Proviron-treated animals (group A) were significantly (P < 0.05) higher when compared to the Control-group B; *P<0.05.

Figure 2. Light Micrograph Showing the Cross-Section of the Caudal Epididymis of the Control Animal at X 100 Magnifications



Shown are evidence of numerous regularly shaped epididymal tubules with normal basement and epithelial heights present. In addition, most of the epididymal tubular lumens were filled with spermatozoa with evidence of active spermatogenesis seen in the X100 control animal slides.

Figure 3. Light Micrograph Showing the Cross-Section of the Caudal Epididymis of the Proviron Treated Animal at X 100 Magnifications

Displayed are evidence of numerous atrophic abnormal epididymal tubules with a fewer spermatozoa within their tubular lumens. Moreover, there were a lot of distortions in the tubular structures during development with some degree of abnormal luminal dilatation, gradual reduction in epithelial heights of some of the tubules and widening of interstitial spaces observed in the proviron treated animal slides (X100).

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