ORIGINAL ARTICLE

Cytokeratin-7 signature in the prostate of total and sub-capsular orchidectomized wistar rat following experimentally-induced benign prostatic hyperplasia: a comparative study

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Abstract

Background: Evidences to establish superiority between Total orchidectomy (TT orchi) and Sub-capsular orchidectomy (SC orchi) as surgical interventions for prostatic enlargement are scarce. Cytokeratins have high specificity profile as benign and tumor markers. *Aim and Objectives*: To compare the outcomes of TT orchi and SC orchion Benign Prostatic Hyperplasia (BPH). *Material and Methods*: Fifteen adults male Wistar rats (140-200 g) were grouped into three (A-C) n=5. Group A is the control while B and C received 10 mg/kg testosterone intramuscularly to induce BPH for 10 days. After that, Group A underwent sham surgery, B, TT orchi and C, SC orchi. Surgeries were performed under ketamine (5 mg/kg) and 2-0 chromic was used. Rats were observed for 14 days post-surgically after which they were sacrificed under anesthesia. Blood samples were collected for biochemical assays. Histological and immunohistochemical analyses were done. Data were analyzed using One-way ANOVA and Student Newman-Keuls. Results were presented as Mean ± SEM, $p \leq 0.05$ was significant. *Results*: SOD and CAT were raised in both TT orchi and SC orchi. Prostate Specific Antigen (PSA) was reduced significantly in SC orchi compared to TT orchi. Cytokeratin7 reactivity was positive in TT orchi but negative in others. *Conclusion*: SC orchi may be considered over TT orchi as BPH surgical therapy.

Keywords: Total Orchidectomy, Sub-capsular Orchidectomy, Cytokeratin 7, Benign Prostatic Hyperplasia

Introduction

Prostatic diseases are significant health burdens and are the third most expensive urological diseases in the USA, the UK and probably the most common urological disorders in Africa [1-2]. It is also one of the common diseases in elderly men which will continue to rise as a result of decline in fertility and increase in life expectancy [3]. Despite the prevalence of Benign Prostatic Hyperplasia (BPH), its pathogenesis is not well understood. Several overlapping theories have been proposed, majority of which are operative in nature. Men castrated before puberty do not develop BPH [4] and, in men with genetic disorders that inhibit androgen production or androgen action, prostatic growth is impaired [5-6]. Ageing has been implicated as the central mechanism overtime; recent novel findings also highlighted the key role of hormonal alterations, metabolic syndrome, and inflammation [7-8]. About 20–30% of men reaching 80 years of age require surgical intervention for the management of BPH [6]. The pathogenesis of both prostatic

cancer and BPH do overlap and medical castration is usually being employed at advanced level [4]. However, the cosmetic effect of medical castration on the patient is a big concern. Androgen deprivation by orchidectomy or removal of the testis has become the mainstay of hormonal treatment of carcinoma of the prostate since 1941 with reported good effects [9-10]. Though recent report has it that Prostate Specific Antigen (PSA) measurement as a diagnostic tool for prostate-related diseases has limitation due to its organ specificity and not being disease-specific [11]. Total orchidectomy which leaves the scrotum empty, is however unacceptable to some patients because of loss of self-image, religious and cosmetic reasons. Sub-capsular orchidectomy, introduced by Riba in 1942 is more acceptable [12]. Authors differ in their reported clinical outcome with both methods, with claims of superiority of one over the other [12-14]. The present study, therefore, aims to ascertain which of the two methods is more effective and can be patient-friendly in the case of advanced prostatic enlargement using rat model due to paucity of data.

Material and Methods

Animal care and management

Fifteen adults male Wistar rats weighing 140 to 200g were procured, housed and cared for in the Animal House facility, Babcock University Ilishan-Remo, and used for this research. The rats were housed in clean plastic cages under natural light and dark cycles and at room temperature. They were then randomly grouped into 3 (A, B & C) of n=5, and were left to acclimatize for a period of 7 days. They were fed on normal rat chow and had free access to water *ad libitum*. Group A served as the control while group B and C are the TT and SC orchidectomized groups respectively following BPH induction. This research was approved by Babcock University Health Research Ethics Committee with reference number BUHREC 069/19.

BPH induction

Testosterone propionate was obtained in its formulated form from Sigma Aldrich, USA, stored in amber bottles and refrigerated. The experimental groups were administered 7.5 mg/kg testosterone propionate by intramuscular injection using a 2ml syringe. The administration regimen was as follows:

Table 1: Showing the groupings of the rat and the various treatment given to each group

Group	Animals	Dose	Rationale
A	5	Intramuscular injection of normal saline (0.5ml) for 10 days	Control
B	5	Intramuscular injection of testosterone propionate (7.5mg/kg) for 10 days	To induce BPH
C	5	Intramuscular injection of testosterone propionate (7.5mg/kg) for 10 days	To induce BPH

Blood sample collection for PSA test (baseline test)

Blood samples were obtained by ocular puncture prior to the surgical operation in all the rats to measure the levels of PSA before orchidectomy.

Orchidectomy operation procedure

Intramuscular injection of Ketamine (5mg/kg) was administered to each rat and kept in the cage until fully anaesthetized. It took an average of 5-6 minutes to achieve full sedation. The rats were placed in a supine position and restricted with plaster tapes to maintain stability. Rats in group A underwent sham surgery. For group B, the scrotum was cleaned using ethanol antiseptic solution. Midline incision was made in the scrotum and the testes, epididymis and spermatic cord were dissected out. For group C, the tissues within the testicles were scooped out from the tunica vaginalis (Figure 1). The incision was closed in layers using an atraumatic 2.0 chromic suture and then painted with methylated spirit.

Post-operative care

The rats were returned to their cages and allowed free access to feed and water into which paracetamol (100 mg/kg) was dissolved to serve as analgesia for the rats. The rats were left for 2 weeks. The effect of TT and SC orchidectomy on feed and water intake and other parameters were measured within the space of two weeks.

Animal sacrifice

After a period of 2 weeks, the rats were anesthetized and the inguinal region of the rats were incised and cut open. The prostate gland was excised from the rats, weighed and fixed in 10% formalin for histological studies. Blood was collected into plain bottles through cardiac puncture and centrifuged to obtain serum for biochemical assays.

Figure 1: Showing the whole testis and the epididymis removed in total orchidectomy and the testicular content scooped out in sub-capsular orchidectomy

Biochemical assays

The blood samples obtained were collected into plain sample bottles and centrifuged at 3000 rev/min. for 30 minutes to separate sera. Prostate Specific Antigen (PSA), Testosterone, Thiobarbituric Acid Reactive Species (TBARS), Superoxide Dismutase (SOD) and Catalase (CAT) levels were determined using an Enzyme-Linked Immunosorbent Assay (ELISA) kit according to the manufacturer's instructions (ALPCO Diagnostics, Salem, NH, USA). The absorbance was measured at 450 nm using a mircroplate ELISA reader (Bio-Rad Laboratories, Inc.).

Special stains protocols

Masson's trichrome and Verhoeff's stains were done according to modified previous methods [15].

Immunohistochemical protocol for cytokeratin 7

Immunohistochemistry of the prostate was done to demonstrate the expression of cytokeratin7 using a previous method [16].

Photomicrography

LEICA DM 750 microscope connected to a digital camera (LEICA ICC50) and a desktop computer was used to view the slides.

Statistical analysis

We presented results as Mean ± Standard Deviation (SD). One-way ANOVA was used to analyze data, followed by Student Newan-Keuls (SNK) test for multiple comparisons. GraphPad Prism5 (Version 5.03, GraphPad Inc.) was the statistical package used. The results were considered significant when $p < 0.05$

Results

Table 2: Showing the initial body weight, final body weight, absolute prostatic and relative prostatic weights of orchidectomized rats following BPH induction

Treatment group	Initial BW (g)	Final BW (g)	Absolute prostatic weight (g)	Relative prostatic weight (%)
A	162.8 ± 7.809	198.3 ± 6.862	0.19 ± 0.018	0.0940 ± 0.007
B	166.7 ± 95.742	198.9 ± 7.737	0.42 ± 0.044*	0.2100 ± 0.019*
C	156.6 ± 6.603#	190.0 ± 4.391#	0.43 ± 0.110*	0.2275 ± 0.057*

*# = $p < 0.05$ when compared with the control, * = $p < 0.05$ when compared with the control*

Body and prostatic weights

There is a significant body weight gain across the groups in the final body weight ($p < 0.05$) when compared with the initial body weight. There is a significant increase in both the absolute and relative prostatic weight in both TT orchi and SC orchi groups when compared with the sham groups ($p < 0.05$).

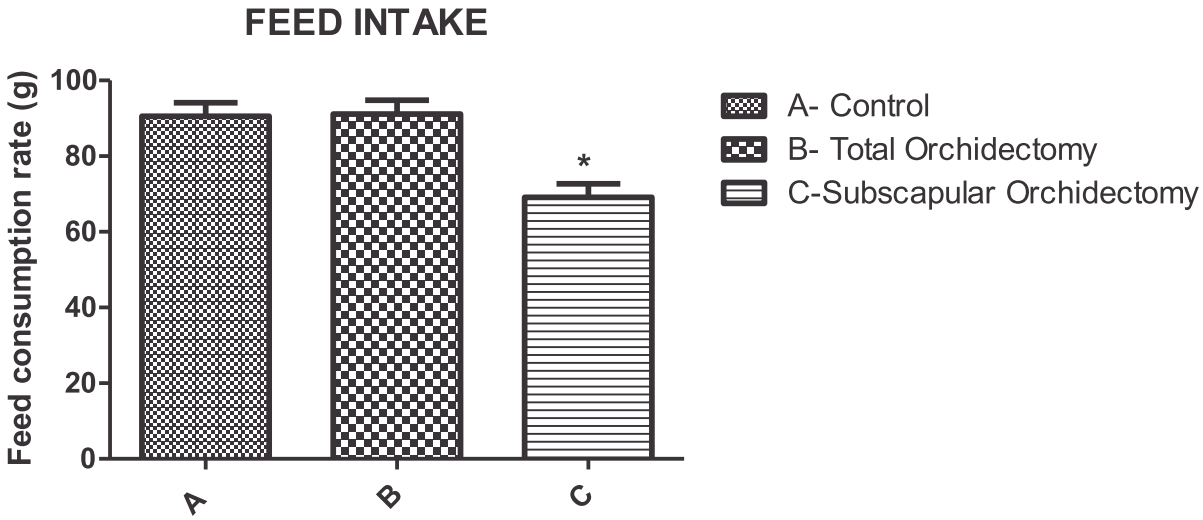

Figure 2: The bar chart shows a significant reduction in feed intake in the SC orchi group when compared with the sham and the TT orchi groups ($P < 0.05$)

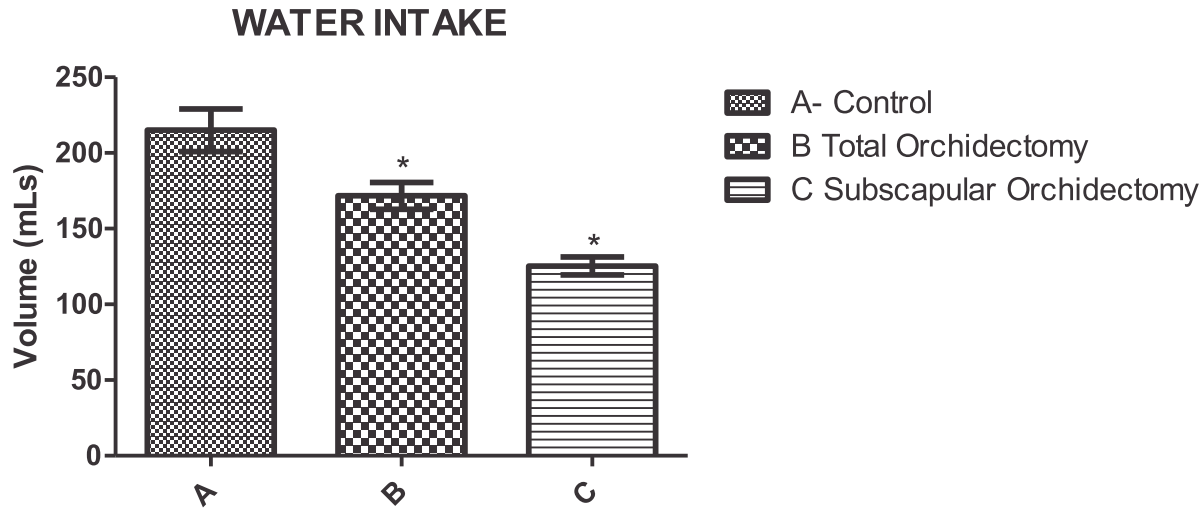

Figure 3: The result shows a significant reduction in the volume of water intake in the TT and SC orchidectomized groups when compared with the sham group ($P < 0.05$).

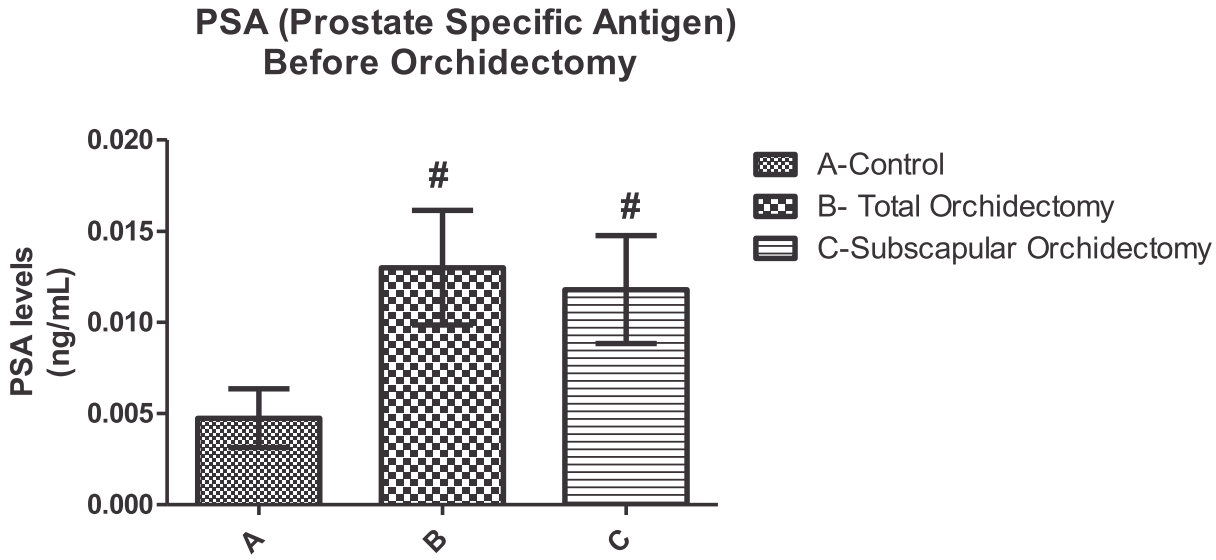

Figure 4: The PSA level was measured across the groups following BPH induction. The result shows a significant increase in the levels of PSA in groups B and C ($P < 0.05$) prior to orchidectomy when compared with the control (group A)

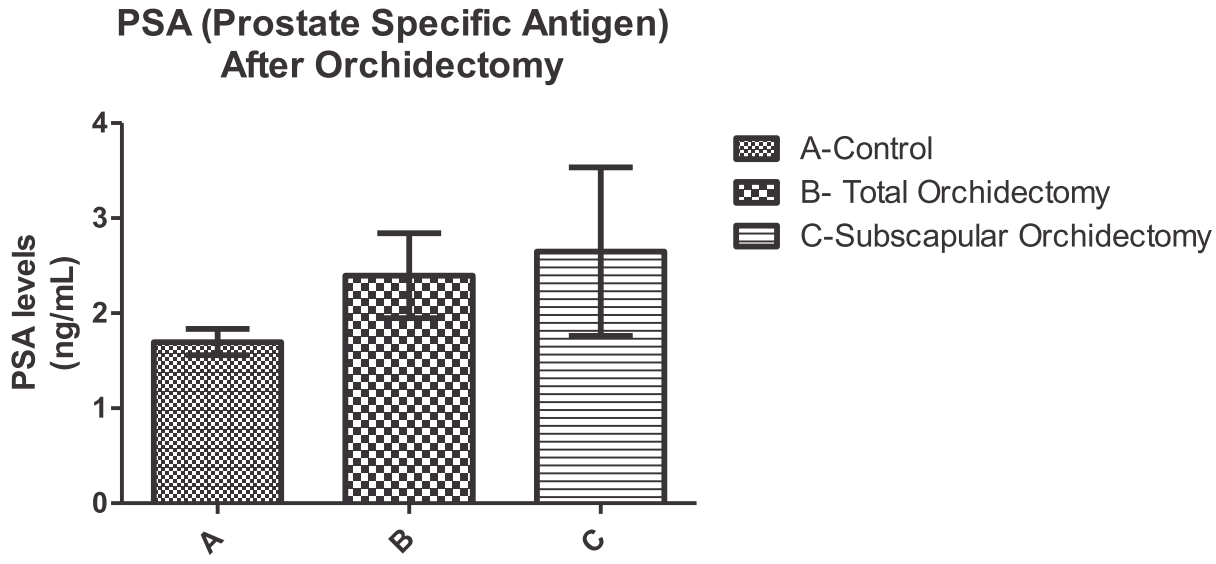

Figure 5: The PSA levels were measured across the groups after orchidectomy in order to deduce its effect on the levels of PSA. The result shows an observable reduction in the total group when compared with the sub-capsular group, though not significant

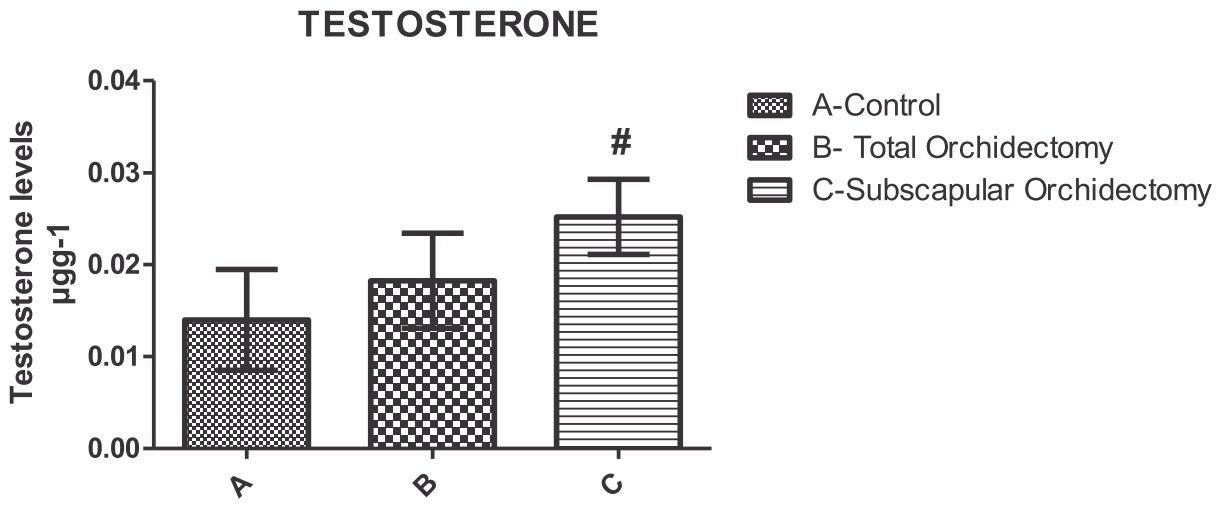

Figure 6: Shows a significant increase in the level of serum testosterone in the SC orchi group when compared with the control and the TT orchi groups (P < 0.05)

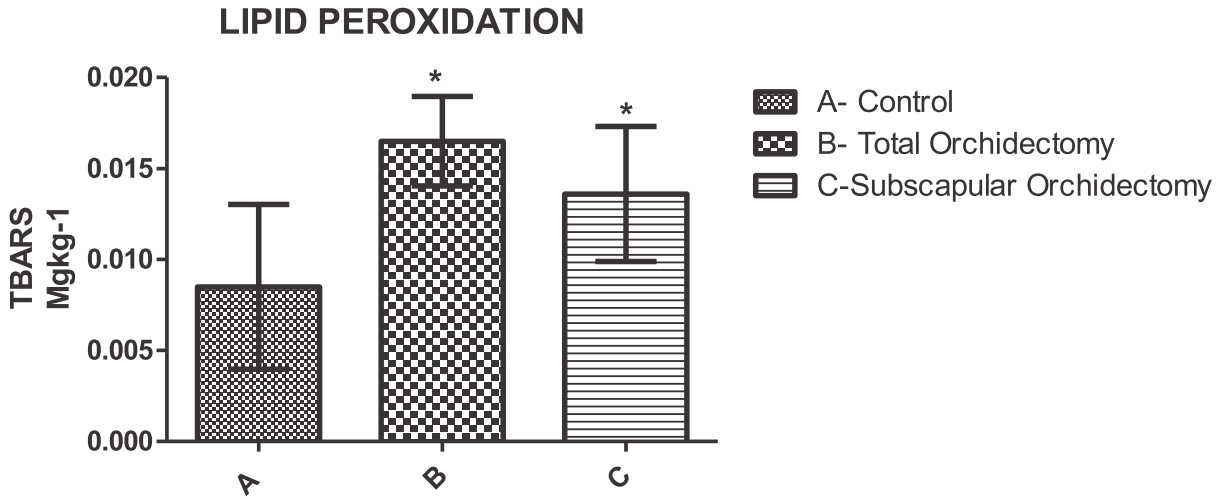

Figure 7: Shows the result of the measurement of the levels of malonaldehyde (MDA) as indicator for lipid peroxidation across the group. There is a significant increase in the levels of lipid peroxidation in the TT orchi and SC orchi groups when compared with the sham group (P < 0.05)

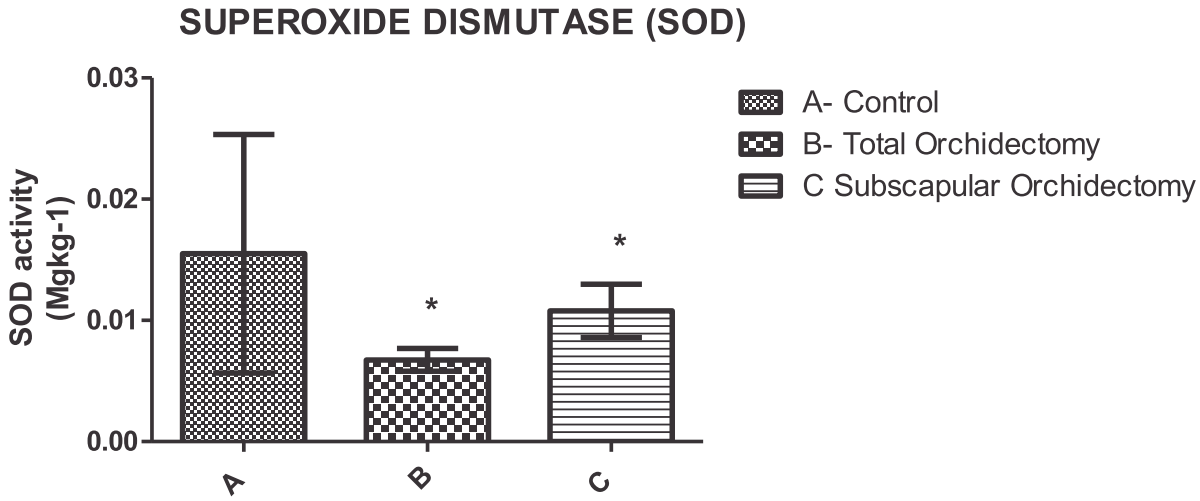

Figure 8: Shows the result of the measurement of the levels of SOD across the group. There is a significant reduction in the levels of SOD in the TT orchi and SC orchi groups when compared with the sham group (P< 0.05)

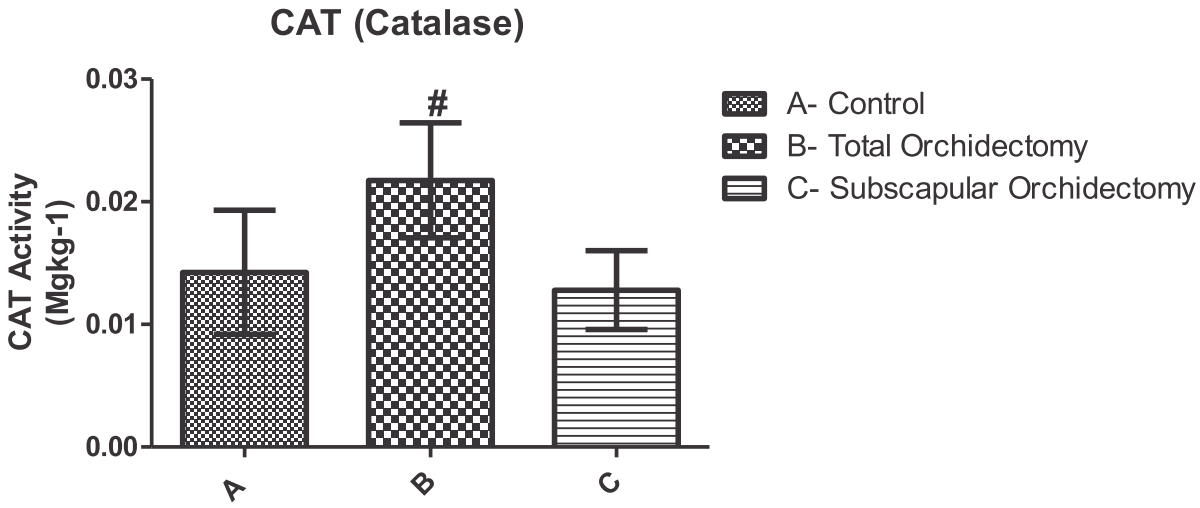

Figure 9: Shows the result of the measurement of the levels of CAT across the group. There is a significant increase in the level of CAT in the TT orchi group when compared with the sham and the SC orchi groups (P< 0.05)

Histopathological results
Haematoxylin and Eosin stain

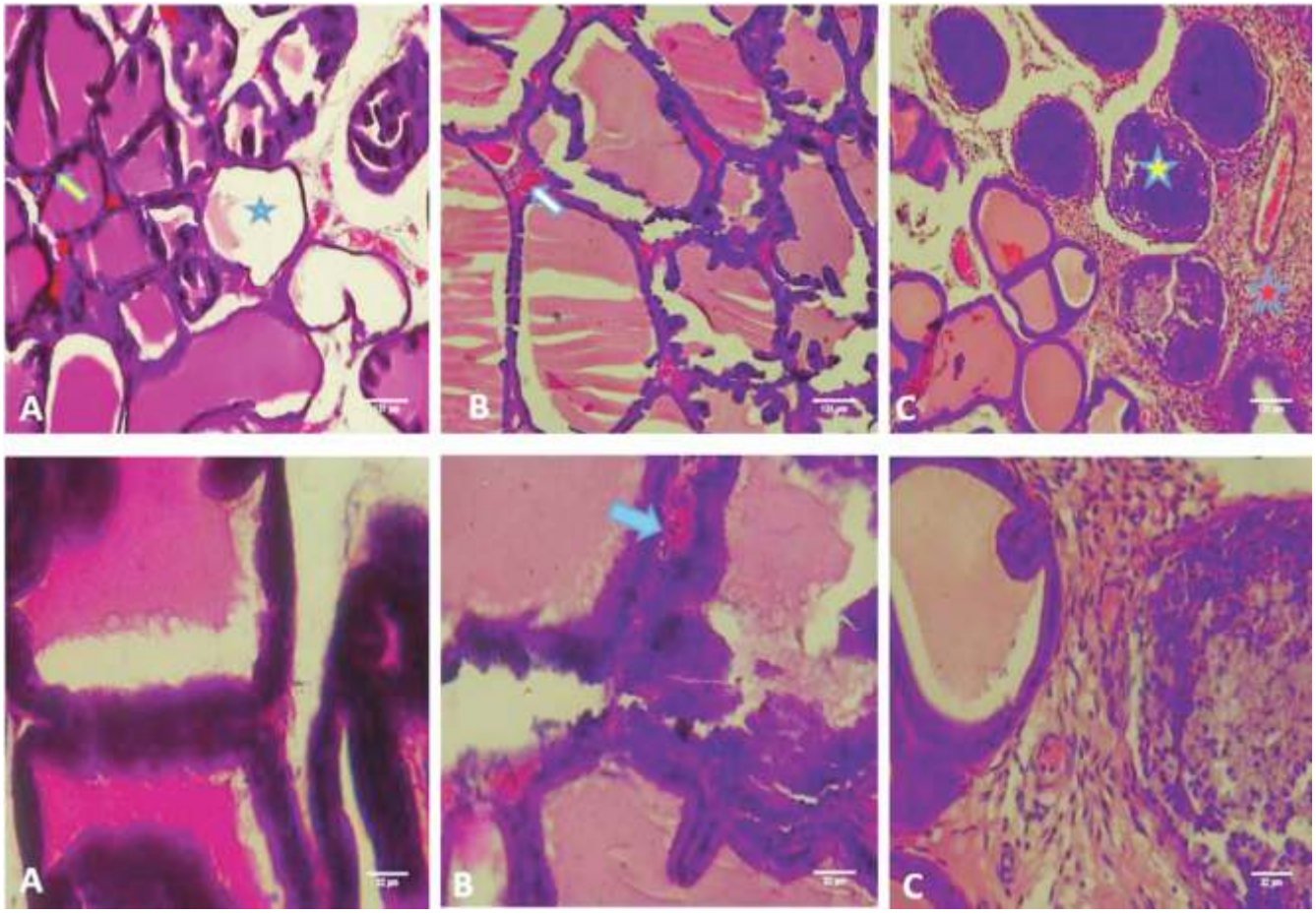

Figure 10: H&E stain of the prostate

Group A shows normal histoarchitecture with normal epithelial thickness (yellow arrow, upper slide) and almost completely clear lumen (star) when compared with the other groups. Group B presents with vascular haemorrhage around the stroma (white arrow, upper slide). The epithelium can also be seen increased in thickness (blue arrow, slide below). Group C shows necrotic glands (yellow star) and distorted stroma (red star). H & E, Scale bars are 131µm and 32µm above and below respectively.

Verhoeff's stain

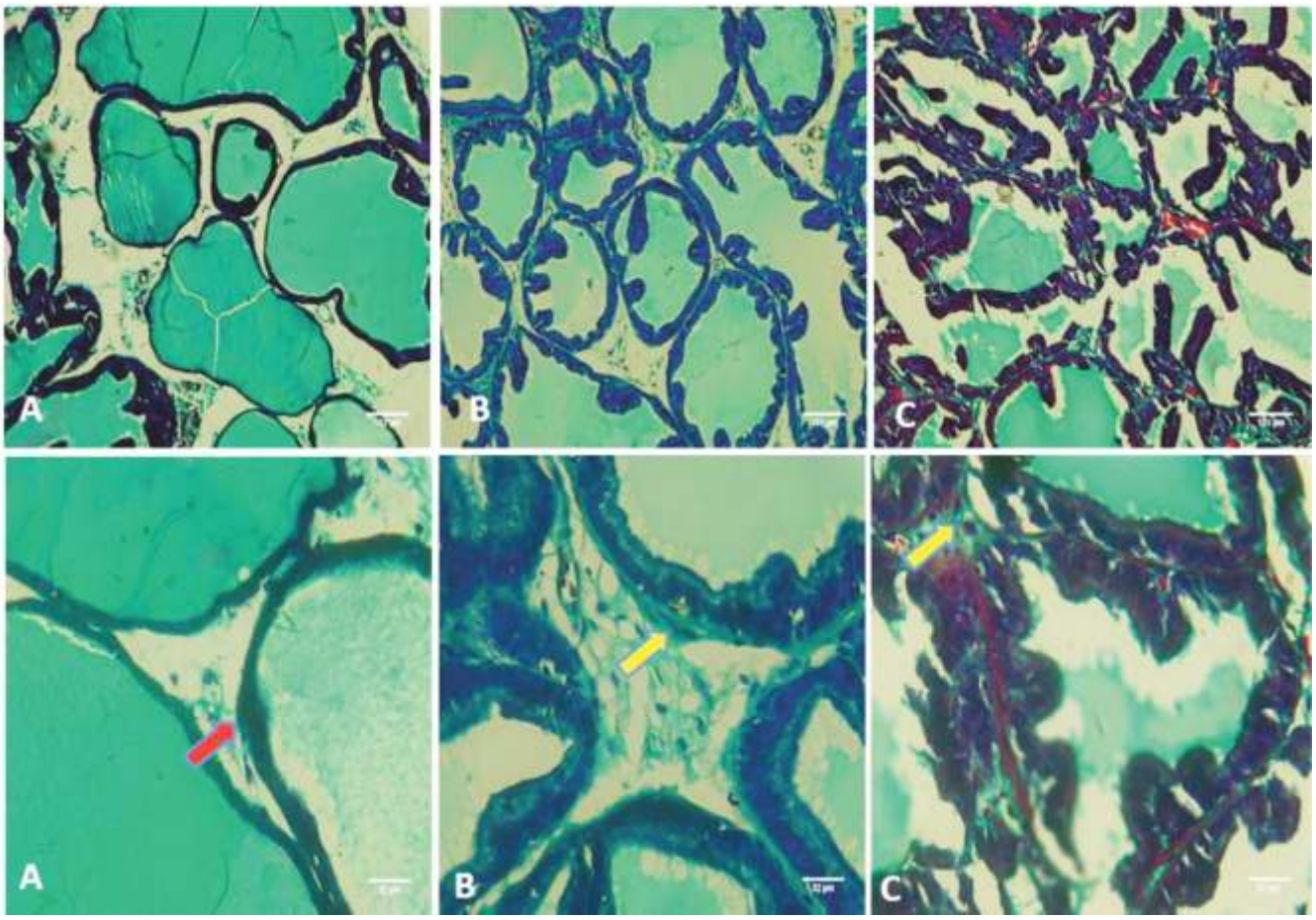

Figure 11: Verhoeff-Van Gieson stain of the prostate

Group A shows moderately distributed collagen fibres in the junction between the epithelium and the stroma of the gland (red arrow) while densely distributed amount of collagen fibres shown in group B and C (yellow arrows). Verhoff's van Gieson. Scale bars are 131µm and 32µm above and below respectively.

Masson's trichrome

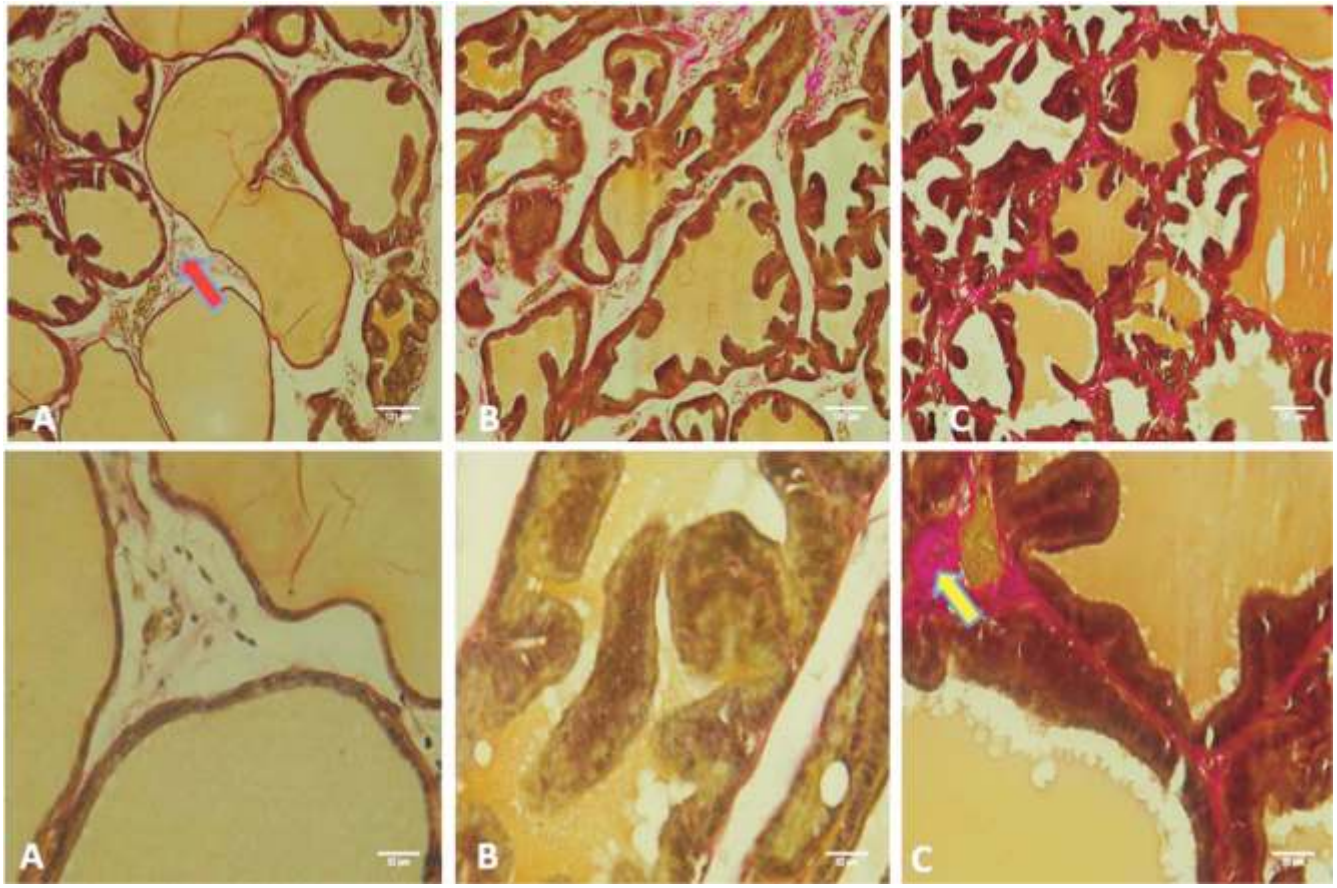

Figure 10: Masson Trichome stain of the prostate

Group A shows moderately stained and evenly distributed elastic fibres, group B also presents elastic fibre content close to that of group A while group C shows densely stained elastic fibres alongside its thickened epithelium. Masson's trichrome. Scale bars are 131µm and 32µm above and below respectively.

Immunohistochemistry: Cytokeratin 7

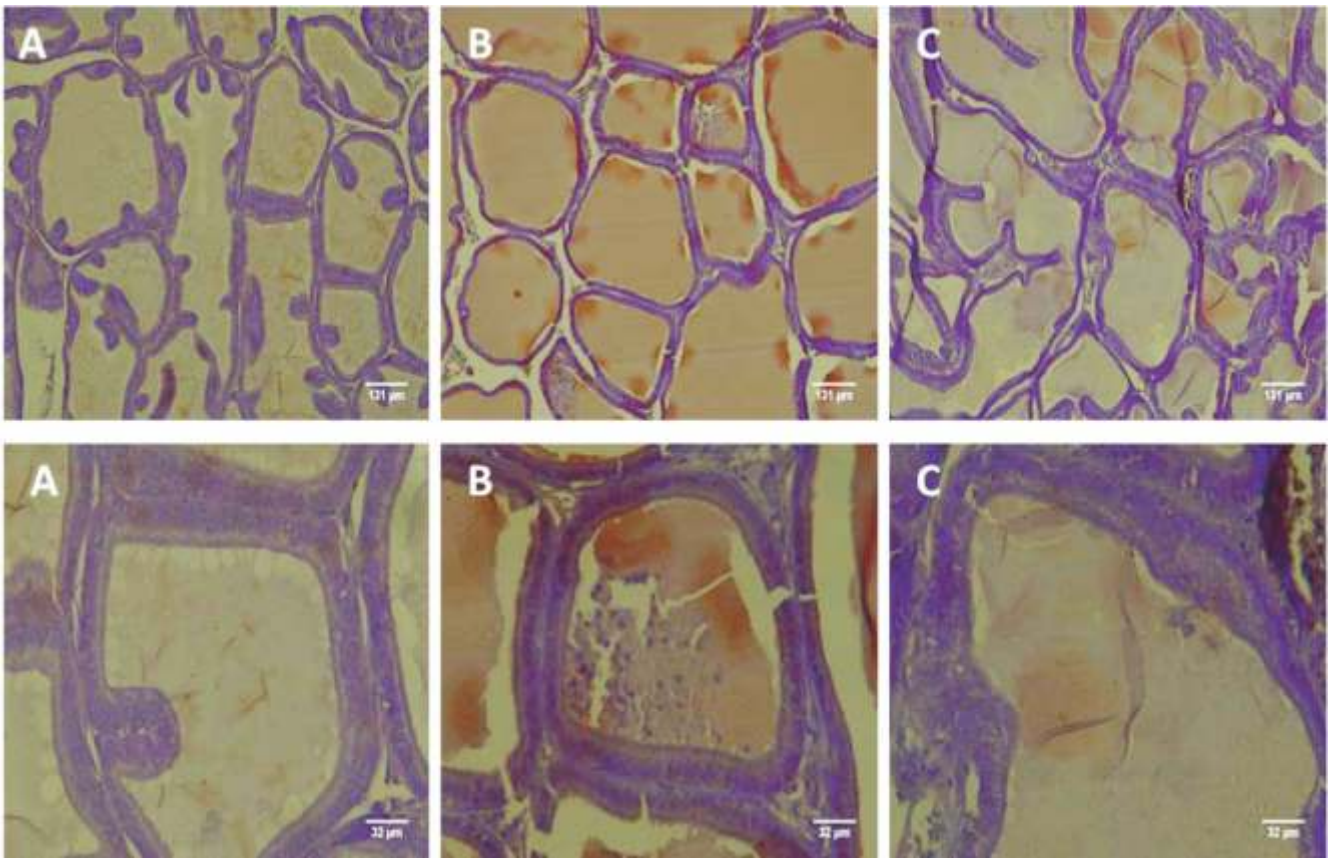

Figure 13: Cytokeratin 7 in the prostatic tissue

Photomicrograph showing the expression of Cytokeratin 7 in the prostatic tissue of Wistar rats subjected to orchidectomy following BPH induction. Group B (TT orchi) shows strong positive reactivity while the control (sham) and group C (SC orchi) stained negative. Scale bars are 131µm and 32µm above and below respectively.

Discussion

With the level of increase in the age of men, there is high tendency for the increase in the rate of prostatic diseases, most especially benign prostatic hyperplasia and prostatic carcinoma. The patho-physiology of these two diseases usually coexists and overlaps. Though many therapies are evolving to manage BPH, there are side effects that come with them aside some ineffectiveness. There is therefore the need to apply combined therapies especially in the case of an advanced BPH secondary to prostatic carcinoma. Orchidectomy (i.e. medical castration) has been employed in many decades ago has a therapy for BPH [17], but the cosmetic effects of the process on the patients are major concerns [9]. In this present study, we try to compare the outcome of TT orchi and SC orchi in testosterone propionate-induced BPH in order to ascertain which one is more effective and patiently friendly using rat model.

We investigated the effect of orchidectomy on the body weights of the rats and the result shows significant increase in the final body weight when compared with the initial body weights (Table 2) as against previous report [18]. Our present finding might be attributable to the anabolic activity of testosterone. Our result also shows a significant increase in the prostatic weight when compared with the control. Proliferation of prostatic epithelial cells accompanies prostate hypertrophy leading to increased area of prostate vesicles [19-20]. We noticed that there was no significant effect of both TT orchi and SC orchi in bringing down the prostatic weight following BPH induction. We measured the food and water in-take in the rats and there was a reduction in food consumption in the SC orchi group when compared with the TT orchi and sham groups (Figures 1 and 2), probably as a result of loss of appetite in the group. The water in-takes in TT orchi and SC orchi groups were also reduced when compared with the sham group.

PSA level is the most frequently employed biochemical parameter in clinical practice used in the differential diagnosis of BPH and prostate carcinoma [21]. We measured the levels of PSA after BPH induction and after orchidectomy in order to see the effect of both TT orchi and SC orchi on its level. The result shows a significant increase in the levels of PSA in TT orchi and SC orchi groups when compared with the control group (Figure 3). This elevation of PSA values shows that testosterone injection successfully induced BPH since PSA is secreted by the epithelial cell of the prostate gland. Thus, abnormal serum level of PSA serves as a direct indicator of prostatic disorder [22]. However, there was an observable reduction in the levels of PSA in both orchidectomized groups, though not significant (Figure 4).

Increased prostate volume has been stated as an important factor inducing elevations in PSA concentrations [23], which also depends on androgen activity of testosterone converted to dihydrotestosterone by the action of 5- alpha reductase enzyme. Following orchidectomy, a decrease in PSA levels is anticipated after a while [24]. Our result shows significant increase in the level of testosterone in the SC orchi group when compared with the TT orchi and sham groups (Figure 5). This elevation in serum testosterone can be attributed to the subcutaneous injected testosterone which was reduced by TT orchi compared to SC orchi.

Previous report has stated that elevation of Malondialdehyde (MDA) serves as a signal to lipid peroxidation and tissue damage which is associated with the development of BPH [25]. Result from the present study shows a significant increase in the levels of lipid peroxidation in both treated groups when compared with the control, and that, TT orchi and SC orchi could not remedy this (Figure 7). The activity of SOD was significantly reduced in the orchidectomized groups when compared with the control (Figure 8) while the activity of CAT was significantly increased in TT orchi group when compared with the SC orchi (Figure 9). The reduction in the activities of these antioxidant enzymes is attributable to the evoked oxidative stress which is part of BPH pathophysiology. Lipid peroxidation has also been reported to lower antioxidant levels in BPH [26].

Conventional light microscopy has been reported to give important information on the prostate epithelium and stromal characteristics [27-28]. The result from the H&E staining in the present study for the demonstration of histoarchitecture shows normal histology of the control group while the treated groups revealed thickened prostatic epithelium with signs of vascular hemorrhage around the stroma (Figure 10). It has been reported that under low levels of testosterone, it is well recognized that the prostate suffers structural changes, with modifications in its acinar epithelium, basement membrane, elastic fibers and collagen [29-30]. There is the presence of densely distributed collagen fibres in the TT orchi and SC orchi groups as demonstrated using Verhoff's van Gieson stain (Figure 11). Elastic fibres were moderately distributed in the TT orchi group while it is densely distributed in the SC orchi (Figure 12). This shows that elastic fibre integrity is well preserved in the SC orchi group compared to the TT orchi group.

Cytokeratins (CKs) are complex family of intermediate filament proteins which comprises more than 20 different polypeptides that are present in benign and malignant epithelia cells, but may also be present in non-epithelial cells and normal tissues [31]. The expression of CKs is generally confined to epithelia and their neoplasms [32, 33], however, they are not specific tumor markers as others like PSA. The highly diverse expression patterns of CKs have been correlated with different pathways of epithelial differentiation, and thereby allow the accurate and sophisticated classification of epithelial cells into different subtypes [34]. We looked into the expression of cytokeratin 7 (CK7) in the prostate tissue in this present study to see the effect of TT orchi and SC orchi on the protein filament following BPH induction. TT orchi group shows strong positive reactivity (as shown by the brownish coloration) when compared with the SC orchi group. The sham group on the other hand is negative (Plate 4). It has been reported that during cell transformation and tumor development, the specificity of CKs is largely conserved [35]. The diverse and unique expression of CK 7 and CK 20 in carcinomas has also been found to be useful in the differential diagnosis of some carcinomas of epithelial origin [36]. Therefore, the result from our study shows that SC orchi was able to restore the integrity of the prostate following BPH with respect to CK7 expression.

Conclusion

In this present study, we looked into several parameters in order to establish the more effective, less damaging and more subject-friendly procedure between TT orchi and SC orchi as surgical therapies for BPH. It was observed that the two processes showed both efficiencies and deficiencies which are overlapping when it comes to remedying the prostatic integrity in BPH. However, the result from CK7 which seems more specific makes us conclude that SC orchi may be considered over TT orchi as a surgical therapy in a case of advanced BPH, as it gives the patient a sense of high self-image when cosmetic factors are being considered.

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