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Research Article

Impact of SGLT2 Inhibitors on Induced Benign Prostatic Hyperplasia in Rats

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ABSTRACT

Benign prostatic hyperplasia (BPH) is a non-cancerous proliferation of the prostate tissue, predominantly impacting the transitional zone and periurethral area, resulting in lower urinary tract symptoms in elderly males. Chronic inflammation plays a widely acknowledged significant role in the etiology of BPH. Current pharmacological interventions comprise 5-alpha-reductase inhibitors and alpha-adrenergic antagonists, both of which are linked to considerable adverse effects. Thus, there is an increasing demand for alternate therapy modalities with reduced adverse effects. Sodium-glucose co-transporter-2 (SGLT2) inhibitors were initially developed for glycemic regulation in type 2 diabetes mellitus while also providing benefits in diminishing significant cardiovascular incidents, enhancing heart failure results, and decelerating the advancement of chronic renal disease. Recent research indicates that SGLT2 inhibitors have anti-inflammatory and antiproliferative properties. This study examines the impact of ertugliflozin and empagliflozin on testosterone-induced BPH in rats. BPH was induced in rats with the administration of testosterone enanthate. The treatment groups were administered ertugliflozin, empagliflozin, and finasteride. Prostate mass, prostate index, serum testosterone concentrations, and histological alterations were assessed. Ertugliflozin, empagliflozin, and finasteride significantly ($P < 0.05$) decreased mean prostate weight, prostate index, and blood testosterone levels. Histological investigation revealed a reduction of testosterone-induced BPH to mild prostatic hyperplasia in the ertugliflozin and finasteride groups. However, mild-to-moderate prostatic hyperplasia was observed in the empagliflozin group. Both SGLT2 inhibitors, ertugliflozin and empagliflozin, exhibited efficacy in alleviating BPH development, indicating a possible role in BPH therapy. Additional research is necessary to clarify their specific processes in BPH and clinical relevance.

Keywords: Benign prostatic hyperplasia, testosterone, ertugliflozin, empagliflozin, finasteride

INTRODUCTION

Benign prostatic hyperplasia (BPH) denotes the non-malignant proliferation of prostate tissue and is a prevalent etiology of symptoms related to the lower urinary tract in elderly male individuals. The prevalence of the disease has been demonstrated to rise with age, especially in low- and middle-income countries.[1] The primary pathological feature of BPH is the excessive growth and restructuring of epithelial and fibromuscular structures in the prostate's transitional zone surrounding the urethra, leading to prostatic enlargement.[2] Chronic inflammation's significant role in the pathophysiology of BPH is now becoming evident and is regarded as a crucial element in the onset and progression of BPH.[3]

Following lifestyle adjustments, pharmacotherapy is typically the primary approach for managing symptomatic BPH.[4] The gold standard for treatment consists of two classes of drugs: alpha-adrenergic blockers and 5-alpha-reductase inhibitors.[5] As a result, there is growing interest in developing safer alternatives to the current BPH medications.[5,6]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors have been authorized for the management of type 2 diabetes mellitus.[7] These drugs lower blood sugar levels by blocking the action of the kidneys' tubules.[8] In addition to their main effects, they exhibited significant anti-inflammatory effects proved by the reduction in cardiovascular complications,[9] heart failure with low ejection fraction,[10] non-alcoholic hepatic steatosis,[11] and persistent kidney problems.[12]

Furthermore, these drugs demonstrated advantageous anti-proliferative properties implicated in reducing the risk of cancers.[13] Studies highlighted an association between molecular components of diabetes and BPH,[14] which

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encouraged investigating the impact of SGLT2 inhibitors in the management of BPH. Accordingly, this study was designed to investigate the potential effects of SGLT2 inhibitors on the progression of BPH in rats.

MATERIALS AND METHODS

A total of 30 adult male albino rats aged 9–12 weeks were used in this study. The rats were maintained under hygienic conditions in the animal house of (The Animal House of Hawler Medical University, College of pharmacy). The rats were provided with food and water freely. After an acclimatization period of 2 weeks, the rats were randomly allocated into five equal groups (six rats in each group) as follows:

- Group CN: Control negative group was given a placebo.
- Group T-CP: BPH-induced control positive group testosterone (3 mg/kg)
- Group T-Ertu: BPH-induced group, administered ertugliflozin (10 mg/kg)
- Group T-Empa: BPH-induced group, administered empagliflozin (10 mg/kg)
- Group T-Fin: BPH-induced group, administered finasteride (0.44 mg/kg).

BPH was induced by subcutaneous (SC) administration of testosterone enanthate (Panpharma, Germany®) at a dose rate of 3 mg/kg for 28 days, according to El-Shafei *et al.*[15] The drugs ertugliflozin, empagliflozin (Sami pharmaceuticals, Pakistan®) and finasteride (Accord healthcare, UK®) were given daily at a dose rate of 10 mg/kg for both ertugliflozin[16] and empagliflozin according to Malínská *et al*.,[17] whereas finasteride was given at 0.44 mg/kg according to Jawad and Jasim.[18]

Testosterone enanthate ampoule was diluted in olive oil, whereas ertugliflozin, empagliflozin, and finasteride were dissolved in distilled water and given daily by oral gavage to their allocated experimental groups for 8 weeks after 28 days of inducing BPH. The BPH-inducing agent, testosterone enanthate, was given daily to the positive control group as well as to the treatment groups for the whole period of the experimental protocol. The CN group was given an SC injection of olive oil and distilled water orally as a placebo.

The body weight of each rat in different groups was recorded weekly, commencing the experimental study. After 8 weeks of the application of the treatment protocol, the rats were euthanized by intraperitoneal administration of ketamine (90 mg/kg) and xylazine (40 mg/kg) according to Abdulla and Al-Okaily,[19] blood samples were withdrawn by cardiac puncture from each rat, and their serum was used for investigations of testosterone levels (Rats Kit for enzyme-linked immunosorbent assay; Sunlong Biotech, China; catalog NO. SL0668Ra) was used for serum testosterone levels determination (sensitivity of the method was 0.01 ng/mL with intra-and inter-assay variability of <10% and <12% respectively), and their prostates were carefully isolated and weighed to assess for hypertrophy.

The prostate index (PI) was obtained by equation (1):[20]

$$PI = \frac{Prostate\,weight\quad (PW)}{Body\,weight\quad (BW)} \times 100 \qquad (1)$$

The percent inhibition of hyperplasia (PIH) was calculated from the relative prostate weight, as shown in equation (2):[21]

$$PIH = 100 - \left[\left(\frac{Treated\,group - Normal\,control\,group}{Positive\,control\,group - Normal\,control\,group} \right) \times 100 \right] \qquad (2)$$

The prostates were dissected out, and a tissue sample was obtained, fixed in formalin for histopathological examination of prostate tissue.

The study was approved by the ethical committee of the Hawler Medical University, College of Medicine (Meeting code: 2; Paper code: 12; Date: 14/11/2024).

Statistical analysis of data was performed using Statistical Package for the Social Sciences (version 30), and the data are expressed as mean ± standard error of the mean. One-way analysis of variance was used to compare the statistical differences between the groups. Differences are considered significant at the level of $P \leq 0.05$.

RESULTS

The mean body weight, prostate weight (PW), and prostate index (PI) across study groups are presented in Table 1. The average body weight of the rats did not exhibit statistical significance ($P > 0.05$) across all experimental groups [Table 1].

Figure 1 illustrates the impact of administering ertugliflozin, empagliflozin, and finasteride over an 8-week period on the mean PW and PI across various experimental groups.

The testosterone-induced BPH (T-CP) group had significantly ($P < 0.05$) higher mean PW and PI [Figure 1] compared to the CN-placebo group. In contrast, the mean PI of the BPH-induced group treated with ertugliflozin (T-Ertu), the BPH-induced group treated with empagliflozin (T-Empa) and finasteride group (T-Fin) were non-significantly ($P > 0.05$) different than those of CN-placebo group. Rats in the BPH-induced group treated with ertugliflozin (T-Ertu), empagliflozin (T-Empa), and finasteride (T-Fin) exhibited a significantly reduced ($P < 0.05$) mean PW and PI compared to the testosterone-induced BPH (T-CP) group, as illustrated in Table 1.

The mean serum testosterone levels are displayed in Table 2. Statistical analysis indicated a significant ($P < 0.05$) elevation in mean serum testosterone levels in the BPH-induced positive control group compared to the CN, T-Ertu, T-Empa, and T-Fin groups, respectively. The groups administered ertugliflozin, empagliflozin, and finasteride exhibited a non-significant ($P > 0.05$) difference in mean serum testosterone levels as compared to the CN group.

The histological section [Figure 2a and b] depicts an image of the prostate gland from the CP group with hormonal-induced hyperplasia of the prostate, demonstrating pronounced BPH features, including significant hyperplasia of the epithelial lining, irregular micropapillary projections within the gland's lumen, and notable stromal expanding accompanied by blood vessels congestion.

Table 1: The mean (± SEM) of the prostate profile of BPH-induced (T-CP) rats following daily treatment of testosterone enanthate (3 mg/kg) for 12 weeks, then treated with either ertugliflozin (10 mg/kg), empagliflozin (10 mg/kg), or finasteride (0.44 mg/kg) for 8 weeks post-BPH induction

Group	Body weight (g) Mean±SEM	Prostate weight (g) Mean±SEM	Prostate index (%) Mean±SEM
CN	341.17±27.16[a]	1.19±0.11[acde]	0.35±0.03[acde]
T-CP	334.83±17.30[a]	2.15±0.19[b]	0.64±0.05[b]
T-Ertugliflozin	325.17±21.75[a]	1.39±0.13[acde]	0.43±0.03[acde]
T-Empagliflozin	301.17±20.05[a]	1.42±0.04[acde]	0.48±0.04[acde]
T-Finasteride	326.50±13.31[a]	1.36±0.06[acde]	0.42±0.02[acde]

Different letters indicate statistical significance at a $P \leq 0.05$. BPH: Benign prostatic hyperplasia, SEM: Standard error of the mean

Table 2: Impact of ertugliflozin, empagliflozin, and finasteride on mean serum testosterone levels in testosterone-induced BPH in rats

Group	CN	T-CP	T-Ertu	T-Empa	T-Fin
Mean±SEM	2.53±0.25[acde]	4.27±0.37[b]	1.97±0.07[acde]	1.91±0.13[acde]	2.69±0.16[acde]

Different letters indicate statistical significance at a $P \leq 0.05$. BPH: Benign prostatic hyperplasia, SEM: Standard error of the mean

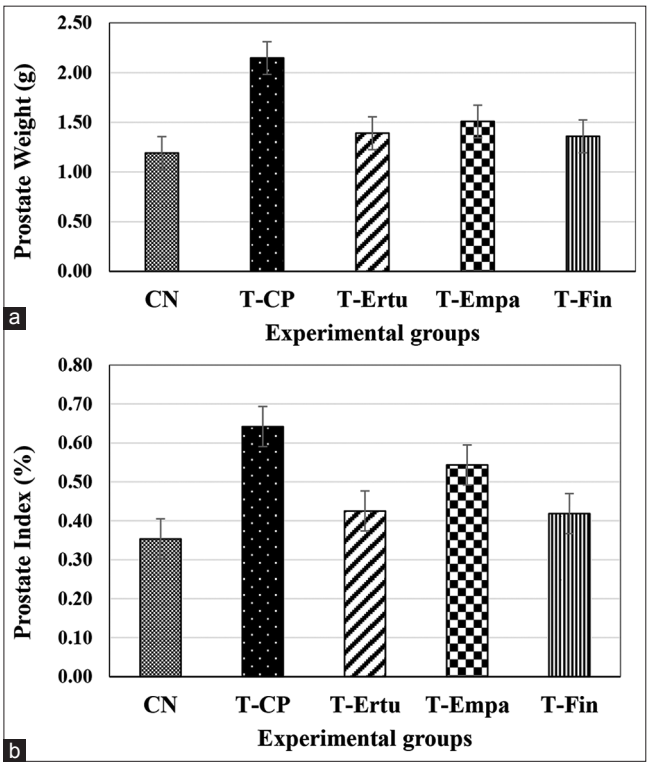

Figure 1: Prostate weight (a) and prostate index (b) in the CN group, testosterone-induced benign prostatic hyperplasia (BPH) positive control group (T-CP), BPH-induced group treated with ertugliflozin (T-Ertu), BPH-induced group treated with empagliflozin (T-Empa), and BPH-induced group treated with finasteride (T-Fin)

The microscopic analysis of prostate tissue from the CN group [Figure 2c] reveals normal prostatic architecture characterized by well-maintained glandular and stromal components. The cell layers of the prostatic glands are intact, the lumen includes a limited number of papillary folds, and the adjacent fibromuscular stroma retains its characteristic architecture. No evidence of abnormal changes, including hyperplasia, inflammation, or fibrosis, is seen, suggesting that the tissue is in its normal physiological condition.

In the conventional treatment, finasteride-treated group [Figure 2d], the severe characteristics of BPH were greatly diminished, evidenced by a marked improvement in both epithelial and stromal hyperplasia, with histological traits nearing normality.

Ertugliflozin treatment resulted in a significant decrease in BPH-related histopathological alterations, evidenced by mild epithelial and stromal hyperplasia and vascular congestion [Figure 2e]. Whereas, the empagliflozin treatment produced mild-to-moderately hyperplastic epithelial cells with papillary projections [Figure 2f].

DISCUSSION

This study explored the potential effects of two SGLT2 inhibitors, ertugliflozin, and empagliflozin, in counteracting the influence of testosterone in promoting the progression of BPH induced in rats.

The non-significant ($P > 0.05$) differences in the mean body weight among the experimental groups align with prior research,[22,23] that also observed no changes in the body weight of testosterone-induced BPH in rats under comparable experimental conditions. However, there is conflicting evidence on the effects of testosterone on body weight related to the dose and duration of administration.[24]

The PW and PI are frequently used to determine the extent of BPH progression.[20] The significant ($P < 0.05$) increase in PW and PI of BPH induced group (T-CP) compared to the CN group in the present study is the consequence of dihydrotestosterone (DHT) activation of androgenic receptors that promote the proliferation of epithelial and stromal cells of prostate.[25] Similar observations have been reported by Shanmugasundaram *et al.*[26] and Alamoudi *et al*.[27]

Moreover, the T-CP group had significantly ($P < 0.05$) higher mean serum testosterone levels than the CN group. These results explain the significant rise in both the mean PW and PI of the T-CP group relative to the CN group ($P < 0.05$) in our investigation. Research has established a significant

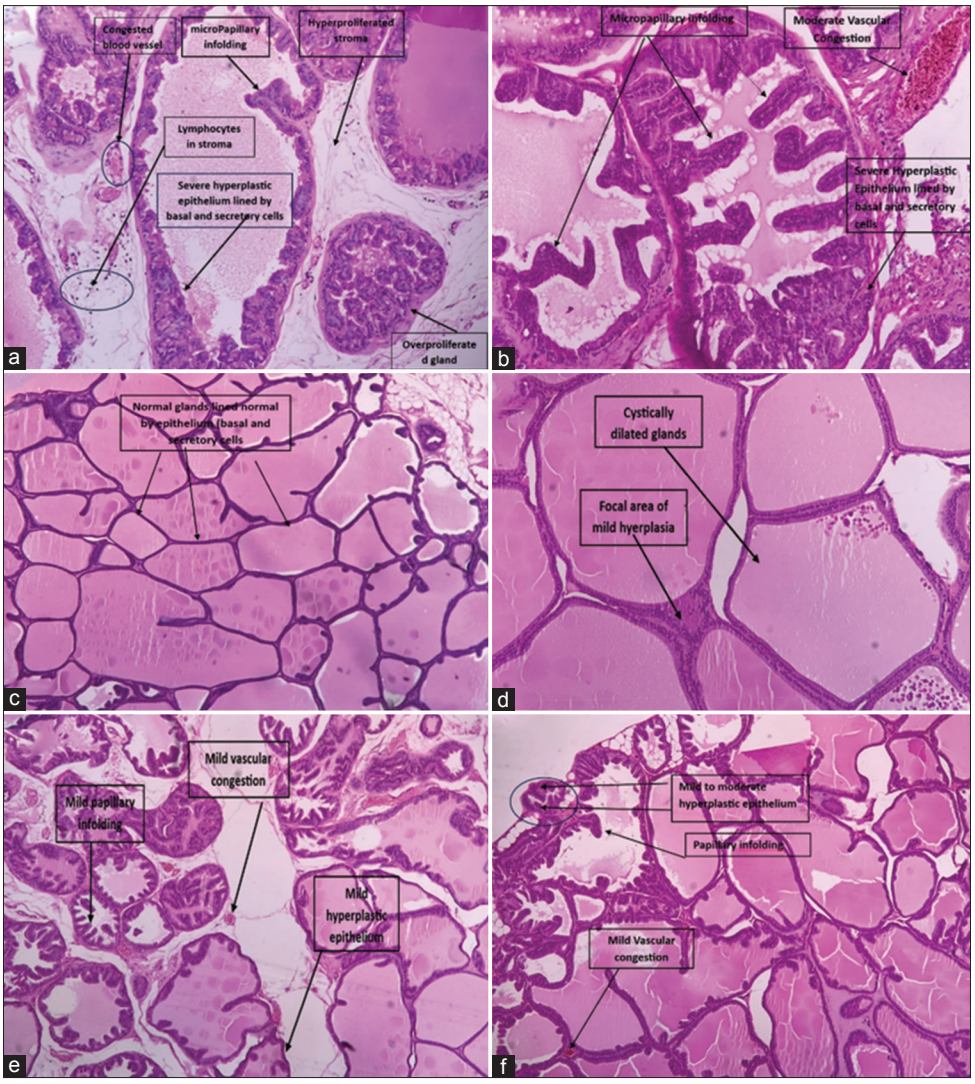

Figure 2: Histopathological sections (×40) of prostate tissues (Hematoxylin and Eosin stain) from rats in the benign prostatic hyperplasia (BPH)-induced positive control group (a anb b), the negative placebo control group (c), the BPH-induced group treated with finasteride (d), the BPH-induced group treated with ertugliflozin (e), and the BPH-induced group treated with empagliflozin (f)

association between circulatory testosterone levels and the extent of prostate enlargement.[28]

The statistically ($P < 0.05$) increased mean serum testosterone level in the T-CP group can be explained by the negative feedback mechanism induced by the continuous administration of exogenous testosterone on the hypothalamic-pituitary-gonadal axis that reduces the production of endogenous testosterone while the serum levels of testosterone remain elevated.[29,30]

The histological changes observed in the prostate segment of the T-CP group compared to the CN group provided further evidence for the significant ($P < 0.05$) higher PW, PI, and serum testosterone levels. The histological examination of prostate sections of the T-CP group showed varying degrees of hyperplastic changes in the epithelial and glandular layers[31] with prominent papillary infoldings.[32] Furthermore, significant edema and elevated fibroblasts within the gland. Enlarged blood vessels and lymphocytic infiltration were also apparent in the stroma, indicating advanced BPH disease[33] in contrast to prostatic sections of CN rats that displayed normal characteristics of prostatic architecture, with well-preserved glandular and stromal components.

Finasteride, a first-line medication for the management of BPH[34] was used in the current study for the purpose of comparison and demonstrated a significant ($P < 0.05$) decrease in the mean PW and PI as well as in the mean serum testosterone levels which coincide with the findings of Elsherbini *et al.*[21] and Shanmugasundaram *et al.*[26] These inhibitory effects of finasteride were further supported by the amelioration of profound prostatic hyperplastic changes to a mild hyperplasia that closely matches with the normal architecture of prostatic tissue upon histological examination, albeit consistently described by Alhussien *et al.*[35]

Administration of both ertugliflozin and empagliflozin resulted in a significant ($P < 0.05$) decrease in the mean PW and PI compared to the T-CP group by 79.2% and 76.1%, respectively. This effect is most probably due to the consequences of the significant ($P < 0.05$) lowering of mean

serum testosterone levels found following ertugliflozin and empagliflozin administration compared to the T-CP group.

These inhibitory effects were more obviously reflected by the mild hyperplasia in the histological sections of the ertugliflozin group, whereas mild-to-moderate hyperplastic changes in the empagliflozin group compared to the prominent prostatic hyperplasia shown in the T-CP group rats.

The significant inhibitory effects indicate that both drugs led to the suppression of the androgenic axis by reducing serum testosterone level, thus decreasing conversion to DHT and inhibiting proliferative signaling factors that contribute to the enlargement of the prostate gland. Similarly, canagliflozin, another SGLT2 inhibitor, has been found to reduce the expression of epidermal growth factor in BPH and to alleviate BPH that has been induced experimentally.[36]

However, it is worth noting that the histopathological sections of the empagliflozin group showed mild-to-moderate hyperplasia in prostate sections. The differences seen in the histological sections between the effects of ertugliflozin and empagliflozin may be due to variances in their physicochemical characteristics, especially their pKa values. These properties affect how well each drug can get into tissues and spread throughout the prostate, which may help explain why they have different effects on prostate histology. Ertugliflozin is more lipophilic than empagliflozin, which promotes better membrane penetration in lipophilic tissues such as the prostate. Since ertugliflozin was classified as a Biopharmaceutical Classification System (BCS) class I drug based on high solubility and high permeability characteristics,[37] while according to the same system (BCS), empagliflozin is a class III drug, which has high solubility but low permeability.[38] This point makes ertugliflozin have higher oral bioavailability, which is 69% in rats,[39] whereas only 31% for empagliflozin.[40] Another influencing factor apart from their anti-inflammatory effects that most likely contributed to the mild hyperplasia seen following ertugliflozin in contrast to mild–moderate hyperplasia observed with empagliflozin in this study is related to differences in their affinity to inhibit SGLT transporters. It was demonstrated that ertugliflozin is more selective to SGLT1 inhibition than empagliflozin,[39] which is upregulated in prostatic diseases such as BPH.[41]

It is also worth noting that the limitations of this study are the number of rats. However, utilizing animal models is found to mimic human disease and is cost-effective, although it requires testing in clinical settings for high reproducibility to validate the effectiveness and safety of SGLT2 inhibitors in the therapy of BPH in human subjects.

CONCLUSION

The present study's findings indicate oral administration of ertugliflozin and empagliflozin at a dosage of 10 mg/kg significantly reduced the progression of BPH by 79.2% and 76.1%, respectively, as demonstrated by decreased PWs, PI, serum testosterone levels, and marked improvement in the histopathological changes in the prostate tissues of testosterone induced-BPH rats. These findings illustrate that SGLT2 inhibitors may have therapeutic advantages beyond glycemic management and could be advantageous in the management of both hyperglycemia and BPH. Further studies are required to investigate their molecular role and clinical significance in managing and alleviating the progression of BPH in the human population. Furthermore, the experiment was performed over a limited timeframe, leaving long-term consequences, such as hormonal and histological alterations unknown. Subsequent research should incorporate prolonged follow-up periods to assess the long-term effects of therapy.

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