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Original Research Article

A Potential Anti-inflammatory Effect of Ertugliflozin in Animal Model

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Abstract: ***Background:*** Acute kidney injury (AKI) accounts for up to 60% of hospitalized patients in intensive care units and is a widespread diagnosis. Recent years have seen an increase in risk factors for it, including old age, chronic diabetes, and kidney disease (CKD). The definition of acute kidney injury (AKI), formerly known as acute renal failure, is a rapid decrease in the glomerular filtration rate. Nephrotoxicity is mainly caused by drugs and auto-immune-induced kidney injury, which is defined by immune cell infiltration in the tubulointerstitial. Interleukin-1B (IL-1B) and tumor necrosis factor-alpha (TNF-α) are signs of kidney inflammation. ***Objective*****:** Evaluate the Anti-inflammatory effect of ertugliflozin. ***Materials & Methods*****:** Thirty adult male albino rats were recruited. These rats were raised in an animal house with a special commercial diet and water. After ten days of acclimatization, the selected rats were separated at random into three groups. Each experimental group consisted of ten rats. This study ran from December 18, 2023, to January 1, 2024, and was carried out in the Animal House of the College of Medicine/University of Babylon. Serum samples were taken for measuring IL-1B and TNF-α. ***Result*****:** The results demonstrated that ertugliflozin provides anti-inflammatory in the treated groups. The two parameters manifest it. ***Conclusion*****:** The results emphasize that ertugliflozin has an anti-inflammatory effect.

Keywords: Ertugliflozin, TNF-α, IL-1B.

INTRODUCTION

In both inpatient and outpatient settings, as many as 60% of patients admitted to intensive care units have the diagnosis of acute kidney damage (AKI). Its incidence has increased in recent years, which is consistent with a rise in risk factors such as kidney disease (CKD), diabetes mellitus, and senior age. Nephrotoxicity is the third most common cause of Acute Kidney Disease (AKD), which has gotten worse in recent decades, according to epidemiological studies. as a result of drug use that carries a higher risk of kidney damage. Studies have shown that up to 20% of critically ill patients use nephrotoxic drugs. While safety tests are required before new pharmaceuticals can be released onto the market, adverse effects are frequently discovered only after the drug is on the market and being used by various populations worldwide. The kidney's excretion of drugs and metabolites exposes the kidneys' high-energy-requiring structures, the glomeruli and tubules, to large concentrations of foreign chemicals, which explains why drug-induced kidney injury rates are so high [1].

Loss of glomerular filtration rate. GFR is a late sign of renal impairment, and additional indicators are being studied to allow for early management, perhaps improving the prognosis of these patients. Although high-quality studies prove no benefit, there are some promising candidates:

1. KIM-1, or Kidney Injury Molecule, is an adhesion molecule generated in the proximal convoluted tubule (PCT). It has been shown that in cases of ischemia and drug toxicity, KIM-1 is elevated in urine concentration. This has been reliably established for cisplatin, gentamicin, and cyclosporine, and in some cases, it is raised 48 hours after the hazardous agent is administered and before GFR declines.
2. The production of beta-2 microglobulin, primarily by lymphocytes, raises the concentration of the protein in urine in inflammatory conditions, such as infections and autoimmune illnesses. It is thought to be a sign of tubular damage after glomerulus filtration and PCT reabsorption. A study on kidney transplantation showed a high degree

of accuracy in differentiating rejection in patients with calcineurin inhibitor (CNI) toxicity before the decline in kidney function.

3. A protein called clusterin is present in many organs, including the kidney, and it plays a role in both apoptosis and antiapoptosis processes. It is not filtered and is created in the tubules during stressful conditions to stop cell death. Compared to creatinine, its higher diagnostic accuracy for tubular damage has been shown using cisplatin, vancomycin, tacrolimus, and gentamicin. It does not rise in patients with glomerular injury and has an early increase comparable to that of KIM-1.
4. All nucleated cells produce the protein cyclostatin C, which can be freely filtered. Since the proximal tubule entirely reabsorbs it, it is typically utilized to estimate GFR in cases with steady renal function, such as those involving cirrhosis, when creatinine clearance is less accurate. Research on renal toxicity has demonstrated a stronger association between amphotericin B, polymyxin, vancomycin, and cisplatin than with creatinine [2].

SGLT2 inhibitors, often known as glucose-lowering medicines, work by decreasing the amount of glucose reabsorption from the renal filtrate, producing a glucosuric effect and eliminating excess glucose. Since the first SGLT2 inhibitor was introduced in 2012, the class of drugs has expanded to include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin in the Americas and Europe, with more drugs in the class starting to gain traction in other countries. Despite being intended to help with type 2 diabetes body weight control and lower hyperglycemia, it is now recognized that SGLT2 inhibitors offer additional treatment alternatives to address the comorbidities and cardio-renal consequences associated with type 2 diabetes. Nephroprotective impacts of SGLT2I are class effects seen in individuals with normal or reduced GFR while using any of the approved medicines [3].

Aim of the Study

1. Investigate the effects of ertugliflozin on inflammatory biomarkers (Tumor necrosis factor-alpha and interleukin-1Beta) in male rats.

MATERIALS AND METHODS

Forty adult male albino rats aged between 10 and 12 weeks, weighing 250-300 g, were enrolled. These rats were habituated under an animal house maintained in 14-hour light-dark cycles provided with a specific type of commercial diet and water. The selected rats were randomly divided into four groups after ten days of acclimatisation. Ten rats were involved in each group of experiments. This study started from 18/12/2023 to 1/1/2024 and was conducted at the Animal House in the College of Medicine/University of Babylon. The selected rats were divided randomly into four groups, with ten rats in each group as follows:

Group A is controlled negative and received only Normal saline I.P. for 14 days.

Group B is controlled positive and received 10mg/kg of methotrexate (MTX) I.P. on day 10 of the experiment.

Group C is the treated group and received 20mg/kg of ertugliflozin orally by gavage for 14 days + 10mg/kg of MTX was given I.P. on day 10 of the experiment [4].

The rats were euthanized at the end of the experiment on day 15 with xylazine (10 mg/kg) and ketamine (75 mg/kg). The serum samples were taken through the rat's abdomen, and the diaphragm and rib cage was cut off so the heart could be seen. Then, a 5cc syringe was used to draw blood directly from the heart, which was slowly poured into a gel tube to avoid hemolysis. Serum samples were deposited in a plain tube and refrigerated at 2-8C for biochemical analysis using ELISA kits for TNF-α and IL-1B.

Ethical Approval

The publishing ethics committee at the College of Medicine, University of Babylon in Iraq, authorized this work. A local ethics committee evaluated and approved the study protocol, subject information, and consent form (document 4-14). The document date was August 8, 2023.

Statistical Analysis

Mean ±SD was used to express the data. One-way analysis of variance was used to determine the statistical significance of the differences between the different groups (ANOVA). The Statistical Package for Social Sciences (SPSS) version 28.0 program was used for the statistical analysis. When a p-value was less than 0.05, it was deemed statistically significant.

RESULT

Table 1: Biochemical variables in the studied groups

Dependent Variable	Group A N=10	Group B N=10	Group C N=10
TNF-α ng/l	115.8±8.77	139.4±9.63**	124.3±17.9 *
IL-I Beta ng/ml	6.4±1.07	8.32±1.06 **	7.13±0.833 *

*significant (P- value <0.05); ** highly significant (p<0.001). GA is controlled negative (only NS was given for 14 days); GB is controlled positive (10mg/kg of MTX was given I.P. on day 10); GC is the treated group (20mg/kg of ertugliflozin was given for 14 days +10 mg/kg MTX was given I.P. on day 10)

Interleukin-1 Beta (IL-1B) Biomarker:

Results (n=10) are expressed as the mean (± SD). This figure shows a highly significant increase in IL-1Beta level in the B group compared to the A group. However, in group C, IL-1Beta levels decreased significantly compared to those in the B group.

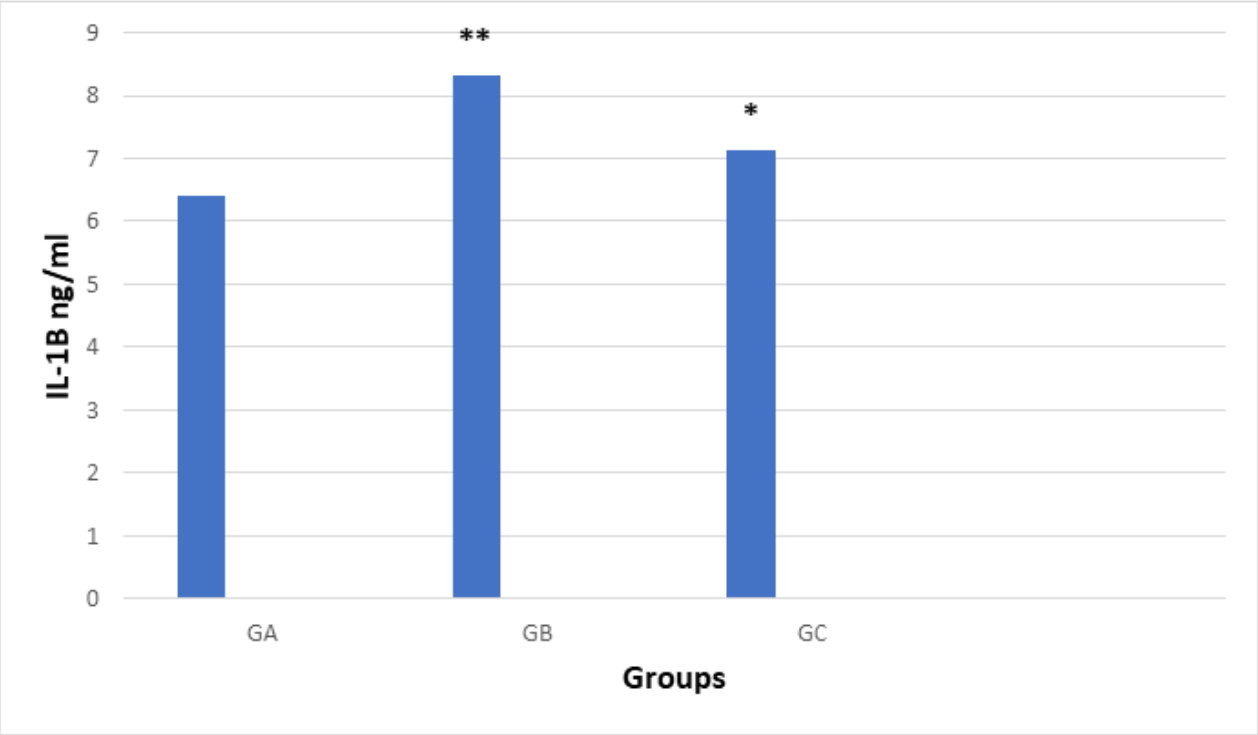

Figure 1: GA is controlled negative (only NS was given for 14 days); GB is controlled positive (10mg/kg of MTX was given I.P. on day 10); GC is the treated group (20mg/kg of ertugliflozin was given for 14 days +10mg/kg of MTX was given I.P. on day 10 of the experiment. (*p<0.05), (p<0.001)**

Table 2: Comparison of treatment effects on IL-1B levels in groups A and B

Dependent Variable	Group	Study group	NO.	Mean ±SD	P- value
IL-1B ng/ml	Group C	Group A	10	6.4 ± 1.07	0.09
		Group B	10	8.32 ± 1.06	0.007

P- value <0.05 is considered significant.

Tumor Necrosis Factor-Alpha TNF-α biomarker:

Results (n=10) are expressed as the mean (± SD). It has been shown that TNF-α level increased highly significantly in group B compared to A group. In addition, in group C, a highly significant decrease in TNF-α was detected compared to the B group.

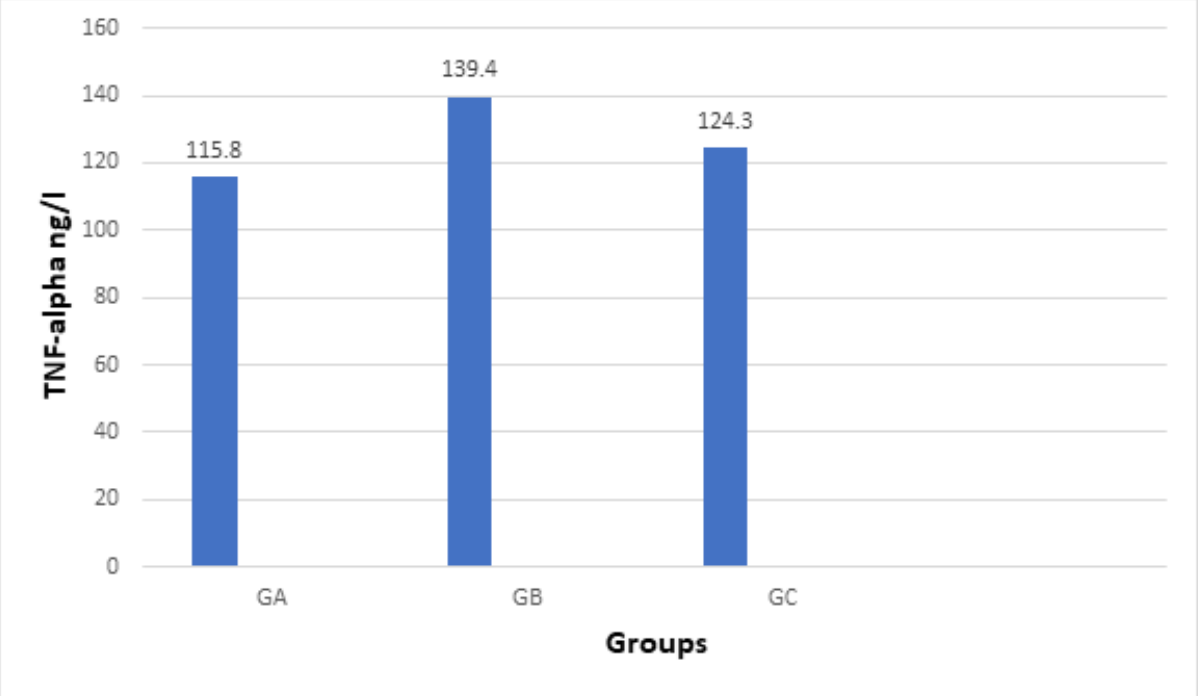

Figure 2: GA is controlled negative (only NS was given for 14 days); GB is controlled positive (10mg/kg of MTX was given I.P. on day 10); GC is the treated group (20mg/kg of ertugliflozin was given for 14 days +10mg/kg of MTX was given I.P. on day 10 of the experiment. (*p<0.05), (p<0.001)**

Table 3: Comparison of treatment effects on TNF-α levels in groups A and B

Dependent Variable	Group	Study group	NO.	Mean ±SD	P- value
TNF-α ng/l	Group C	Group A	10	115.78 ± 8.77	0.101
		Group B	10	139.42 ± 9.63	0.005

P- value < 0.05 is considered significant.

DISCUSSION

This study uses TNF-α and IL-1B as indicators to assess and recognize the anti-inflammatory effect of ertugliflozin on methotrexate-induced nephrotoxicity in male rats.

Increased tumor necrosis factor-alpha (TNF-α) is a marker for inflammation in patients with kidney injury [5]. Also, interleukin-1bata (IL-1B) is a proinflammatory cytokine considered a biomarker for inflammation in case of kidney injury [6]. In the present study, MTX in group (B) causes a significant increase in TNF-α and IL-1B levels as compared to group (A), as shown in Figure (1) and Figure (2), which was in agreement with the previous study [7]. Through its impact on nuclear factor kappa-light-chain enhancer of activated B cell (NF-kB) transcription, MTX can raise levels of TNF-a and IL-1B. MTX prevents the replication of DNA and the growth of all cells, including immune cells. Consequently, adenosine levels drop, which often prevents NF-kB activation. Reduced adenosine levels facilitate the activation of NF-kB, which in turn increases the transcription of pro-inflammatory cytokines such as TNF-α and IL-1β [8]. Pretreatment with ertugliflozin (group C) causes a significant reduction in TNF-a and IL-1B levels compared to group (B), as shown in Figure (1) and Figure (2), which reflected the anti-inflammatory effect of ertugliflozin. These results align with a previous study conducted in 2023, which states that ertugliflozin exhibits its anti-inflammatory effect by inhibiting NF-κB activation [4].

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