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Research Paper

Protective Effect of Trimetazidine on Kidney Dysfunction: A Review of Experimental Evidence

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ABSTRACT

Background and Objectives Acute kidney injury is the main cause of morbidity and mortality in the worldwide that is accompanied by short-term and long-term complications, including chronic kidney disease, end-stage renal disease, and ultimately death. Various mechanisms are involved in renal dysfunction, including oxidative stress, inflammatory responses, apoptosis, fibrosis, and mitochondrial dysfunction. Trimetazidine as a drug with free radical oxygen scavenging property represents to be more invaluable against acute kidney injury. Trimetazidine is considered as an anti-ischemic drug in the treatment of cardiac diseases which has been documented pharmacologic effects such as antioxidant, anti-apoptotic, and anti-inflammatory properties in renal ischemia-reperfusion injury, diabetic nephropathy, and nephrotoxicity models.

Subjects and Methods This review underlines the nephroprotective effect of trimetazidine on kidney injury models. For this review, the articles have been searched in the databases, including PubMed, Scopus, Web of science, and Google Scholar. The search process was provided using these keywords: “Trimetazidine”, “kidney”, “nephrotoxicity”, “renal ischemia – reperfusion injury”, and “Protective.”

Results Present study validates which trimetazidine as a potential agent alleviates kidney dysfunction in experimental models through several mechanisms.

Conclusion Trimetazidine could be considered as promising candidate to treat a variety of kidney diseases in the future.

Keywords Trimetazidine, Oxidative stress, Kidney injury

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Introduction

Acute kidney injury (AKI) is associated with high mortality and morbidity per year and has become a global problem [1, 2]. The long-term consequences of AKI are manifested by chronic kidney diseases (CKD) in patients that ultimately led to end stage renal diseases [2]. The leading causes of AKI include ischemia-reperfusion phenomenon, hypoxia, and toxin agents [2]. Renal ischemia/reperfusion injury (I/R) is known as one of the main outcomes of AKI in the clinic, such as kidney transplantation, renal artery operations, and nephrectomy [3, 4]. There is growing evidence documenting the significant role of reactive oxygen species (ROS) in the pathophysiology of kidney disease, such as renal I/R, nephrotoxicity, and diabetic nephropathy [5-7]. The generation of ROS leads to the opening of mitochondrial permeability transition pore (mPTP) in the inner mitochondrial membrane, initiation of caspase cascade events, inflammatory responses, and eventually, cell apoptosis [5, 8]. Regarding, ROS is a triggering key of these events; therefore, a compound with free radical scavenging property could have a considerable role in inhibiting ROS formation during kidney injury [6].

Trimetazidine (1-[2, 3, 4-trimethoxybenzyl] piperazine dihydrochloride, TMZ), as an anti-ischemic drug, has been used in the treatment of cardiovascular disease. TMZ protects myocardium cells via shifting oxidation of fatty acid to glucose oxidation to preserve adenosine triphosphate (ATP) generation [9]. In addition, TMZ as an mPTP inhibitor, could prevent mPTP opening that inhibits cell death process, indicating a cardio-protective effect in myocardial I/R injury [10]. Primary experimental studies have shown that TMZ results in the improvement of cardiac and kidney function through various molecular and cellular pathways [11-13]. In addition, other pharmacologic properties of TMZ have been documented, including antioxidant, anti-inflammatory, anti-apoptosis, and anti-fibrotic, as well as mitochondrial protection properties in rodent experimental models [6, 14-15].

This review mentions the currently available data from experimental studies that confirm the beneficial effects of TMZ on renal disease models. The results achieved with this drug in the management of renal IR, nephrotoxicity, and nephropathy models will also be explored. Schematic diagram of TMZ has been summarized in Figure 1.

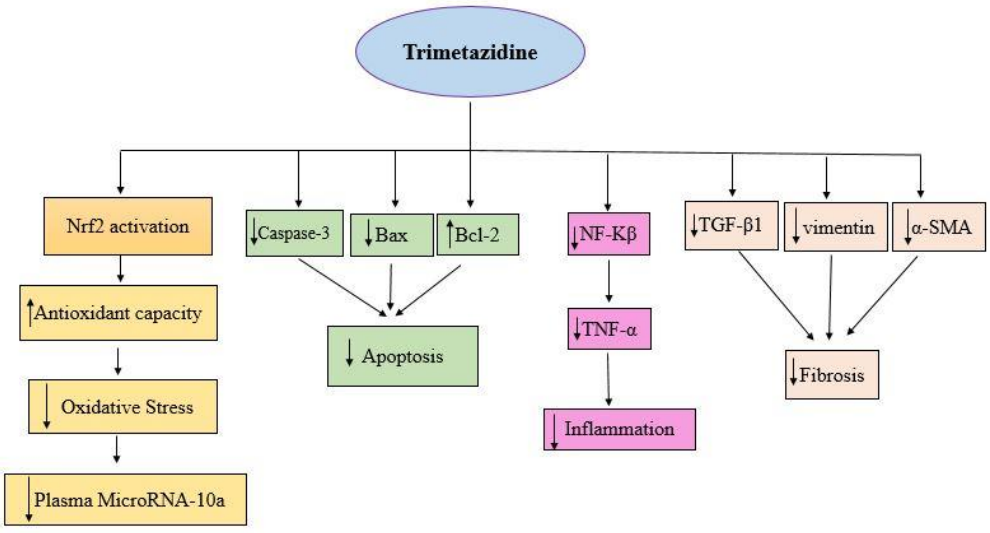

Figure1: Trimetazidine indicated potential protective effect against AKI which related to its antioxidative, anti-inflammatory, antiapoptotic properties via upregulation of Nrf-2 and downregulation of expression of miR-10a and NF-Kβ

Materials and Methods

For this review, original subject-related articles published from 2000 up to July 2021 were reviewed in the PubMed, Scopus, Web of science, and Google Scholar databases. The search process was conducted using these keywords: “Trimetazidine”, “Kidney”, “Nephrotoxicity”, “Renal ischemia-reperfusion injury”, and “Protective.”

Trimetazidine in renal ischemia-reperfusion injury models

I/R injury is a leading cause of AKI, triggering a complex of devastating events, leading to renal cell death and kidney dysfunction [3, 5]. Primary tissue injury occurs during the ischemic period that is associated with the blood supply interruption, followed by reperfusion [5]. Although, reperfusion is an essential time to maintaining blood supply and oxygen delivery, it exacerbates tissue injury [2]. Available evidence proved that reperfusion period results in oxidative injury through ROS mitochondrial formation, as well as caspase cascade activation in renal IR injury [2]. ROS overproduction is accompanied by oxidative stress and the depletion of antioxidant agents, which reduces cellular defense against renal IR injury [4, 17]. Therefore, among the multiple factors that have increased renal I/R injury induced by oxidative stress, the use of a compound to inhibit this event is more valuable [17].

It has been shown that TMZ pretreatment has elevated glutathione (GSH) content, catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) activity and inhibited lipid peroxidation in the rat kidney [18, 19]. In line with this study, treatment with TMZ significantly enhanced the SOD level, and decreased kidney malondialdehyde (MDA) [20]. In addition, TMZ pretreatment before ischemia significantly increased Akt, endothelial nitric oxide synthase (eNOS), and heme oxygenase-1(HO-1) expressions [18]. Likewise, TMZ has been able to enhance hypoxia inducible factor-1α (HIF-1α), which is a defense mechanism against ischemic event and a novel candidate in the treatment of AKI [18, 21]. Regarding this, TMZ could modify nitric oxide (NO) level in warm renal I/R injury model, which is identified as a factor to stabilize of HIF-1α [22]. These findings taken together recommended that TMZ was able to ameliorate renal functional parameters (creatinine clearance and Na^+ reabsorption rate) through modulating HIF-1α / HO-1/ eNOS signaling pathway [18].

Experimental studies reported that I/R injury caused kidney dysfunction via depletion of renal antioxidant levels by excessive ROS production. TMZ administration before the initiation of reperfusion could reduce lipid peroxidation induced by renal IR injury coincided with augmentation of the antioxidant enzymes system (CAT, SOD, and GPx) to cellular protection [12, 23]. Thus, administration of TMZ preserved the enzymatic antioxidant levels, and significantly decreased MDA level, which is the index of lipid peroxidation [12, 23]. These were consistent with an increasing of nuclear factor erythroid 2-related factor 2 (Nrf-2) expression by the TMZ administration in oxidative damage induced by I/R. Nrf-2 is crucial cytoprotective agent in stress situation that protects kidney through adjusting antioxidant agents [12]. Moreover, renal function parameters such as plasma BUN, Cr and glomerular filtration rate (GFR), fractional exertion of sodium as tubular function index ameliorated with TMZ in I/R exposed rats. In I/R rats, caspase-3 was activated, resulting in the activation of Bax protein, and renal cell apoptosis [23]. Apoptosis is identified as main cause of renal I/R injury. TMZ remarkably result in a reduction of Bax mRNA expression, reduced caspase-3 mRNA expression, and increased expression of Bcl-2 [11]. MicroRNA-10a, as renal tissue specific microRNA, is extracted from renal tissue into the plasma against renal cell injury [12, 23]. Treatment of TMZ reduced microRNA-10a in the plasma, indicating a decline in renal cell injury caused by oxidative stress [11].

Post renal I/R treatment of TMZ could impact on fibrosis and apoptosis by inhibition of matrix metalloproteinase (MMP), Bax, and Bcl-2 overexpression in the kidney tissue. These suggest that TMZ exerts its renoprotective effects through anti-fibrotic and anti-apoptotic signaling pathways [24]. In line these studies, the long-term effect of TMZ showed an inhibition of fibrotic agents such as α-smooth muscle actin (α-SMA) and vimentin expressions and a limitation of apoptosis rate which associated with attenuation of significantly changed GFR in renal warm I/R rat model [25]. Histopathological of examination kidney tissue from renal IR rats exhibited a more intense loss of brush

border and proximal tubular injury, indicating tubular necrosis which diminished by TMZ [25]. Prophylactic administration of TMZ before ischemia reduced renal dysfunction confirmed by a diminished BUN, and Cr levels in the serum. Lipid peroxidation and inflammatory mediators such as tumor necrosis factor-α (TNF-α) were suppressed and activation of myeloperoxidase (MPO) in the kidney prohibited by TMZ supplementation. Likewise, TMZ caused replenishment of ATP and GSH in renal tissue that evidenced by the amelioration in histopathological aspects [26]. An experimental study showed that TMZ provided an outstanding role in ATP, and adenosine diphosphate (ADP) synthesis to preserve cell's energy following disruption of mitochondrial membrane caused by kidney I/R injury in rat [27]. Recently, the effect of TMZ on oxidative stress induced by IR in isolated kidney mitochondria displayed a reduction of mitochondrial ROS, MDA content and an increased mitochondrial GSH that would lead to repression of mitochondrial stress pathway [15]. These findings taken together recommended the primary mechanism of TMZ was elevation of antioxidant capacity, and prevention of lipid peroxidation in the kidney.

Nephrotoxicity

Toxicity induced by drug and heavy metals is well known widespread source of AKI [29]. These toxic agents have an important role in induction of nephrotoxicity by ROS production and disturbing of the cellular antioxidant system [30]. The most common pathological findings of nephrotoxicity include glomerular atrophy, tubular cell toxicity, apoptosis, and potential inflammatory response [31].

Trimetazidine in cisplatin nephrotoxicity

Cis-Diammineplatinum (II) dichloride (CSP), is one of the most widely used anti-cancer drugs in malignancy [32]. Excessive side effects of this drug in other organs (Nephrotoxicity, nausea and vomiting, bone marrow suppression, and neurotoxicity) have limited the use of this drug [33]. Among of these complications, the most common side effects of CSP are nephrotoxicity [33]. Overgeneration of free radical oxygen and oxidative stress are main mechanism of CSP nephrotoxicity [31]. Oxidative stress caused by CSP leads to a decrease in the level of antioxidants, especially glutathione, and ultimately accompanied by renal cell impairment [34]. Thus, an antioxidant agent can play a substantial role to scavenge free radical oxygen for protecting cells [35]. Results from primary studies confirm support the hypothesis which TMZ has a nephroprotective effect on CSP toxicity that might be attributed to its ability on enhancing of SOD activity and renal GSH and a decreasing MDA level. In response to oxidative stress, activation of NF-Kβ leads to the generation of inflammatory mediators, consist of IL-6, and TNF-α which was significantly prohibited by TMZ [36].

Trimetazidine in gentamycin nephrotoxicity

Gentamycin is classified as an aminoglycoside antibiotic, is used to treat bacterial infections. Nephrotoxicity is identified as one of the side effects of gentamycin in the clinic. Several studies have shown that gentamycin nephrotoxicity caused by oxidative stress led to renal proximal convoluted tubules injury [37, 38]. Findings of an experimental study indicated that pretreatment with TMZ improved BUN and Cr in the plasma, as well as, excretion of γ-glutamyl transpeptidase and *N*-acetylglucosaminidase enzymes was normal in the urine, indicating the conservation of tubular function [39]. However, the mechanism of TMZ on gentamycin nephrotoxicity has not been investigated. Based on previous study, TMZ might have protective effect on nephrons through antioxidant properties in gentamycin nephrotoxicity [18].

Trimetazidine in cyclosporine nephrotoxicity

Cyclosporine A (CsA) is a major immunosuppressive factor which plays an important role in the autoimmune diseases and survival of the organs after transplantation [40, 41]. However, long-term use of CsA followed by progression of chronic renal failure in the patients [42, 43]. A recent report suggested that oxidative stress is considered as a causative agent in nephrotoxicity induced by CsA [44]. Findings from an in vivo study indicated that TMZ by its removing effects on free radicals could prevent lipid peroxidation formation in a rat model of CsA induced nephrotoxicity. Thus, inhibition of lipid peroxidation was accompanied by improvement of renal function in CsA treated rats evidenced by amelioration of morphological alterations [44]. In contrast to these findings, an experimental study showed that TMZ administration along with CsA led to a reduction of renal function on CsA exposed rats [45]. This

dissimilarity might be related to species differences, gender, and the doses of TMZ and CsA, or nephrotoxicity model [46, 47].

Trimetazidine in glycerol nephrotoxicity

Rhabdomyolysis is a clinical syndrome that results from injury to skeletal muscle and the leakage of muscle cell contents into the extracellular fluid and blood circulation [48]. Rhabdomyolysis is well known as one of the causes of acute renal failure (ARF) [48]. Glycerol induced rhabdomyolysis is an experimental model which is similar to the development of ARF due to trauma or muscle damage in humans, leading to extensively proximal and distal tubular injury [49]. Exploration of an in vivo study confirmed that oxidative stress induced by glycerol increased indexes of renal functional (BUN, Cr, creatinine clearance, urea clearance). In addition to, antioxidant system as a potential defense mechanism, including SOD, CAT, glutathione reductase, and reduced glutathione against stress situation significantly was disrupted. These changes reverted by TMZ via antioxidant properties [49].

Trimetazidine in mercury nephrotoxicity

Mercury is identified as one of heavy metals which its concentration is increasing in the environment [50]. Since the kidney provides an important role in detoxification and excretion of toxic agents, as a result more toxins are concentrated in the kidney. Regarding, proximal tubule cells are vulnerable against pollutants agents and accumulation of this agents in the kidney leads to AKI [51]. One of the most common causes of kidney dysfunction following exposure to toxins is oxidative stress [52]. Renal injury induced by mercuric chloride ($HgCl_2$) demonstrated a reduction of Cr clearance, an elevation of serum BUN and Cr, increasing of urinary flow, and glucosuria that implies renal dysfunction through generation of renal lipid peroxidation and depletion of GSH content [52]. Treatment with TMZ exerted an improvement of kidney function and amelioration of GSH level, indicating a protective effect of TMZ on nephrotoxicity induced by $HgCl_2$ [52].

Trimetazidine in diabetic nephropathy

Diabetic nephropathy (DN) is considered as the main reason of chronic kidney diseases and the prevalence rate of DN is increasing in the worldwide [53, 54]. Streptozotocin (STZ), an antibiotic extracted by *Streptomyces achromogenes*, has been employed in experimental diabetes model via its toxic action on pancreatic β-cells [55]. The primary proposed mechanism to cytotoxic action of STZ is oxidative stress that discharges antioxidative agents, and facilitates free radicals oxygen production [55]. Studies have shown that TMZ was effective in treatment of various diseases, including heart diseases, renal I/R injury, and nephrotoxicity through numerous mechanism such as free radical oxygen eliminating, switching energy metabolism from fatty acid oxidation to glucose oxidation, and anti-apoptosis [12, 14]. In vivo and in vitro studies confirmed that TMZ could conserve kidney functional indicators in diabetic rodent [56]. This preservative effect of TMZ confirmed with a suppression of pathological changes of DN, particularly for renal fibrosis [56]. Epithelial to-mesenchymal transition (EMT) is well known as a main key triggering to tubulointerstitial fibrosis [57]. TMZ ameliorated EMT induced by high fat and high glucose (HFG) via attenuation of oxidative stress in forkhead box O_1 ($FoxO_1$) / sirtuin1 (Sirt1) pathway. Expression of FoxO1 is modulated by Sirtu1 [58]. Sirt1, is an important regulator of cellular energy metabolism that inhibits oxidative stress in AKI [59]. Administration of TMZ result in up regulation of Sirt1 and Sirt3 levels in STZ- induced diabetic rats that confirmed by *in vitro* study. HFG environment elevated acetylation of FoxO1 level and TMZ intervention could reverse this effect. On the other, an increase SOD gene expression was reported by TMZ treatment in diabetic rat but significantly decreased after silencing Sirt1[56]. Nicotinamide adenine denuleatide (NAD^+) is substrate for sirt1, TMZ pretreatment increased NAD^+ and the ratio of NAD^+ to NADH in DN rats which emphasizes that TMZ has a key role in regulating intracellular NAD^+ content [56]. Moreover, transforming growth factor beta (TGF-β1) provided a leading role in renal fibrosis. The interaction of TGF-β with receptors leads to a cellular response by the Smad-dependent pathway. TMZ could significantly reduce TGF-β1experssion and deacetylated of Smad, suggesting antifibrotic effect of TMZ [56]. This reveals that the beneficial mechanisms of TMZ against the kidney injury in diabetic situation are comprised by FoxO1/ROS pathway and TGF-β1/Smad signaling in a NAD^+/Sirt1

dependent manner. An increase in expression of fibronectin, Inducible nitric oxide synthase (iNOS) expression, and proteinuria were seen in STZ-induced experimental model which these disorders could improve by TMZ [60]. In addition, histopathological examination of kidney tissue from diabetic rats displayed the disruption of kidney structure, tubular dilation, and disintegration of brush borders in tubular epithelium which were all relieved by TMZ [60]. Another experimental study proved that oxidative stress displays an outstanding role in the nephropathy caused by diabetes. Also, diminished SOD, CAT activities, GSH content, and an enhancement of MDA level was seen in rat kidney treated by STZ [7]. TMZ notably result in an improvement of kidney function via preserving of the antioxidant system and diminishing lipid peroxidation [7].

In vitro study

In vitro study showed that TMZ reduced E-cadherin, and α-SMA in HK-2 cells. Moreover, TMZ suppressed the generation of ROS induced by high fat and high glucose (HFG) in HK-2 cells. The Sirt1 protein level was diminished in HFG environment, and this alteration was enhanced by TMZ. HFG environment elevated acetylation of FoxO1 level, and TMZ intervention could reverse this effect. TMZ ameliorated EMT induced by high fat and high glucose (HFG) via attenuation of oxidative stress in forkhead box O_1 (FoxO1) / sirtuin1 (Sirt1) pathway. Expression of FoxO1 is modulated by sirtu1. NAD^+ is considered as substrate for Sirt1, the expression of Sirt1 increased with different concentrations of NAD^+ in HFG-exposed HK-2 cells. TMZ increased NAD^+ and NAD^+/NADH levels in diabetic rats. TMZ inhibited ROS signaling to ameliorate EMT in HFG environment through up regulating Sirt1[59].

Conclusion

Based on the mentioned experimental studies, TMZ represents renoprotective properties through antifibrosis, anti-apoptosis, anti-inflammatory, free radical scavenging, and mitochondrial protection effects. However, little research has been done on TMZ effect on various experimental of AKI and CKD. Therefore, TMZ might consider as a potential promising candidate in the prevention and treating a variety of kidney dysfunction after completing the clinical trial phases in the future.

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Conflicts of interest

The authors declared no conflict of interest.

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