ORIGINAL ARTICLE

CONTENTS

Protective effects of coenzyme Q10 in renal ischemia reperfusion injury *via* regulation of Notch-1

Manar H. Mohammed[1], Fadhil A. Rizij[2]
[1]DEPARTMENT OF BASIC SCIENCES, FACULTY OF DENTISTRY, UNIVERSITY OF KUFA, AL NAJAF AL-ASHRAF, IRAQ
[2]DEPARTMENT OF PHARMACOLOGY, FACULTY OF PHARMACY, UNIVERSITY OF KUFA, AL NAJAF AL-ASHRAF, IRAQ

ABSTRACT

Aim: To evaluate nephroprotective effects of coenzyme Q10 in rats with renal ischemia -reperfusion injury by action on Notch-1 pathway.

Materials and Methods: Twenty eight Wistar albino male rats were divided randomly into four groups (each group include seven rats): first one named sham group (just laparotomy, no induction of ischemia), second one named control group (30 min. ischemia/ 2 hours reperfusion), third one named olive oil group (rats injected intraperitoneally. with 0.1 ml olive oil once daily for 2 days, 1 hour after the administration of olive oil in 3rd day renal ischemia was induced), fourth one named Coenzyme Q10 group (rats injected with Coenzyme Q10 (10 mg/kg) intraperitoneally. once daily for 2 days, 1 hour after the administration of Coenzyme Q10 in 3rd day renal ischemia was induced). Kidneys were harvested after 2 hours of reperfusion for assessment of kidney injury molecule-1, interleukin 1 β, TNF α, F2 Isoprostane, glutathione, and caspase 3 by ELISA technique, Notch-1, Jagged-1 mRNA level were assessed by reverse transcription-polymerase chain reaction.

Results: Coenzyme Q10 significantly ameliorated renal ischemia -reperfusion injury as evidenced by the significant reduction of kidney injury molecule-1, interleukin 1 β, TNF α, F2 Isoprostane, and caspase 3 in rat kidneys pretreated with Coenzyme Q10, glutathione level was significantly elevated in rat kidneys pretreated with Coenzyme Q10. Notch-1 and Jagged-1 mRNA expression were significantly decreased compared to control group.

Conclusions: Coenzyme Q10 provide nephroprotection against renal ischemia reperfusion injury owing to its antioxidant, anti-inflammatory, and anti-apoptotic properties, those effects may be linked to the downregulation of Notch-1 and Jagged-1.

KEY WORDS: renal ischemia reperfusion injury, COQ10, Notch-1, Jagged-1

Wiad Lek. 2025;78(10):2101-2109. doi: 10.36740/WLek/210071 DOI

ABBREVIATIONS

RIRI - Renal Ischemia Reperfusion Injury
AKI - Acute Kidney Injury
DGF - Delayed Graft Function
ROS - Reactive Oxygen Species
MAM - Mastermind Transcription Facto
NICD - Notch Intracellular Domain
Hes - Hairy and enhancer of split
Hey - Hairy/enhancer-of-split linked with YRPW motif
NF-κB - Nuclear Factor kappa B
ELISA - Enzyme linked immunosorbent assay

INTRODUCTION

Renal ischemia reperfusion injury (RIRI) considered one of the main causes for AKI [1]. During renal transplantation, RIRI is an unavoidable event that causes delayed graft function (DGF), which leads to the loss of essential kidney parenchyma and primes adaptive immune responses that trigger rejection, ultimately culminating in graft loss [2]. The process of reperfusion in an ischemic kidney exacerbates the oxidative and inflammatory condition leading to DNA and protein damage which finally results in necrosis and apoptosis. The production of pro-inflammatory mediators, activation of apoptotic genes, release of reactive oxygen species (ROS), and calcium excess are the underlying pathophysiological mechanisms [3-4]. The Notch signaling pathway is a highly conserved regulatory pathway that exists in all mammalian cells and originated in Drosophila melanogaster. It is critical for a range of functions, including embryonic development and postnatal tissue homeostasis [5]. It is a key regulator of essential developmental processes such lateral inhibition, lineage decision, and border creation, as well as homeostasis and regeneration in adult tissues [6]. The notch receptors are four in mammals (notch1-notch4) with five notch ligands [Jagged-1, Jagged-2, Delta-like 1

(DLL1), DLL3, and DLL4] [7]. Both the receptor as well as its ligands are transmembrane proteins with abundant extracellular domains. Upon ligand binding to the receptor, a conformational change in the receptor occurs which leads to two successive proteolytic cleavages which result in the release of the intracellular domain (NICD) that translocate into the nucleus and binds to c and the coactivator protein Mastermind transcription factor (MAM) to form a ternary transactivation complex which activates the transcription of notch target genes [8]. The two families of transcriptional factors Hairy and enhancer of split (Hes), which includes HES1 and HES5, and Hairy/enhancer-of-split linked with YRPW motif (Hey), which includes HEY one(HEY1) and HEY two(HEY2), which are the main target genes for Notch [9]. Regardless of CSL, NICD has the ability to engage with the mTORC, NF-κB, AKT, PTEN, or Wnt signaling pathways within the cytoplasm and/or nucleus to control the expression of target genes [10-12]. Although Notch signaling is significantly diminished in the adult kidney, both acute and chronic renal injury have been shown to cause Notch to reactivate [13]. In a study of renal IRI induced in rats, Notch2 and hes-1 was found to be upregulated along with NF-κB2, MCP-1 in addition to apoptosis enhancement [14]. Coenzyme Q10 (CoQ10), sometimes known as ubiquinone or ubidecarenone, is a fat-soluble chemical that resembles vitamin A and is necessary for the transfer of electrons during the oxidative phosphorylation of mitochondria. It serves as an electron transporter between the cytochrome systems and the NADH and succinate dehydrogenases [15] CoQ10 functions as a potent antioxidant that scavenges free radicals, prevents lipid peroxidation in cellular membranes, and promotes the regeneration of tocopherol [16]. It is utilized as a dietary supplement and as a co-therapy alongside medication for various diseases such as diabetes, cancer, muscular neurodegenerative disorders, and cardiovascular diseases [17]. The antioxidant and anti-inflammatory effects of CoQ10 was documented in a study of acute nephrotoxicity induced by cisplatin in rats in which CoQ10 decreased the expression of inducible nitric oxide synthase, caspase-3, NF-κB and p53 in renal tissue [18]. In renal IRI induced in rats, CoQ10 pretreatment for seven days at a dose of 10 mg/kg administered intraperitoneally could considerably lower tissue oxidative stress levels as well as histopathology scores and apoptosis [19], furthermore, Liu et al. stated that CoQ10 nanoparticles enveloped with neutrophil membrane (N-NPCoQ10) treatment significantly improved renal function by decreasing oxidative damage, reducing apoptosis of renal cell , and inhibiting inflammatory response in renal I/R injury mouse model [20], so, the effect of COQ10 in renal ischemia reperfusion injury is still to be elucidated in addition to the molecular pathways by which these effects are mediated. The present study aims to investigate the potential nephroprotective effects of CoQ10 in renal ischemia reperfusion injury for rat model in addition to evaluate the possible role of notch pathway in initiating of these effects.

MATERIALS AND METHODS

ANIMAL PREPARATION AND ETHICAL CONSIDERATIONS

The study was conducted on twenty-eight Wistar albino male rats aged (22-24 weeks), weight range 250-300 g. Animals were kept in the animal house at controlled temperature of 25 ± 2ºC and humidity of 60-65% with 12 hrs dark/light cycle, they had free access to water and standard libithium food.

STUDY DESIGN

After two weeks of acclimatization, the rats were allocated into four groups as follows, (seven rats in each group):

Group 1: Sham group in which rats underwent anesthesia and surgery without induction of renal ischemia.

Group 2: control group in which rats underwent 30 minutes of bilateral renal pedicles clumping to induce renal ischemia followed by reperfusion for two hours

Group 3: Olive oil vehicle group in which rats were injected intraperitoneally (i.p) with 0.1 ml olive oil which is a sufficient volume to dissolve the required doses of coq10. Olive oil was administered once daily for 2 days, 1 hour after the administration of olive oil in the third day renal ischemia was induced for 30 minutes followed by two hours of reperfusion.

Group 4: CoQ10 treatment group in which rats were injected with coq10 (10 mg/kg) dissolved in 0.1 ml olive oil i.p. [21] once daily for 2 days, 1 hour after the administration of coq10 in the third day renal ischemia was induced for 30 minutes followed by two hours of reperfusion.

INDUCTION OF BILATERAL RENAL ISCHEMIA REPERFUSION INJURY

An intraperitoneal injection of mixed solution of xylazine 10mg/kg and ketamine 100mg/kg was used to anesthetize the rats [22], then they were kept in cages at constant temperature to avoid hypothermia. When loss of righting reflex is confirmed, the rats were positioned on their back with the limbs, and tail being fixed with

stickers to ensure their stability during surgery following a midline laparotomy incision, the intestine was retracted and both abdominal cavity and renal pedicles were exposed [23]. The renal pedicles were then isolated, and non-traumatic microvascular clamps were placed around the renal pedicles. The kidney color changed from red to dark purple over one to two minutes which confirmed ischemia. After thirty minutes the clamps were removed and renal blood flow was restored to start the reperfusion phase. The abdominal incision was closed by 3/0 silk suture. After two hours of reperfusion, the rats were anesthetized again and both kidneys were removed. The rats were euthanized by an overdose of ketamine. The left kidney was stored in liquid nitrogen for determination of the experiment parameters.

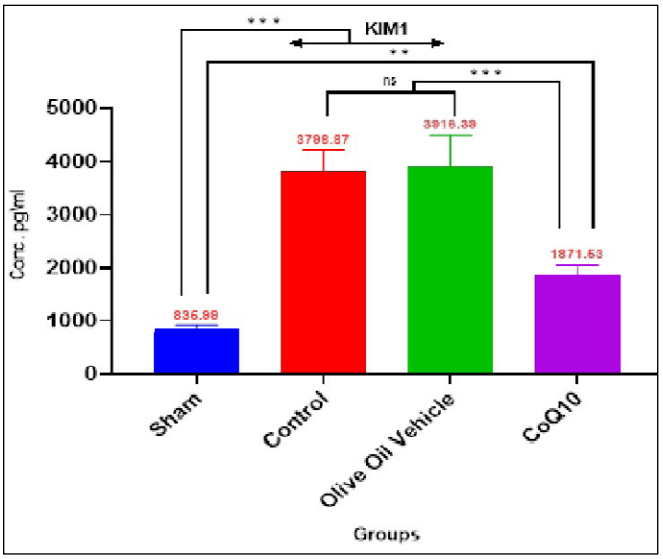

Fig. 1. Error bar chart showing the difference in mean ±SEM values of KIM-1 renal tissue concentration (pg/mL), no. of animals in each group =7, **p< 0.01, ***p< 0.001, non-significant difference
Source: Own materials

ASSESSMENT OF TISSUE KIM-1, IL-1B, TNF A, F2 ISOPROSTANE, GSH, AND CASPASE 3

After the left kidney of each rat was removed, it was washed with cold normal saline to remove any remaining blood clots. Then it was dissected into two halves. One half subjected to homogenization by applying ultrasonic liquid processor of high-intensity in a 1 to 10 (weight by volume) phosphate-buffered saline dilution including a protease inhibitor cocktail and 1% Triton X-100 [24]. Centrifugation at 4°C for 15 minutes at 22,132 × g was then made for this homogenate. The homogenate was then. The supernatant was then collected and divided in Eppendorf tubes for further analysis of KIM-1, IL1β, TNFα, caspase3 and F2 Isoprostane by ELISA technique.

DETECTION OF MRNA EXPRESSION FOR BOTH JAGGED1 AND NOTCH1 BY RT-PCR

To effectively assess the expression level of Notch-1 and Jagged-1 mRNA, we utilized the powerful tech-

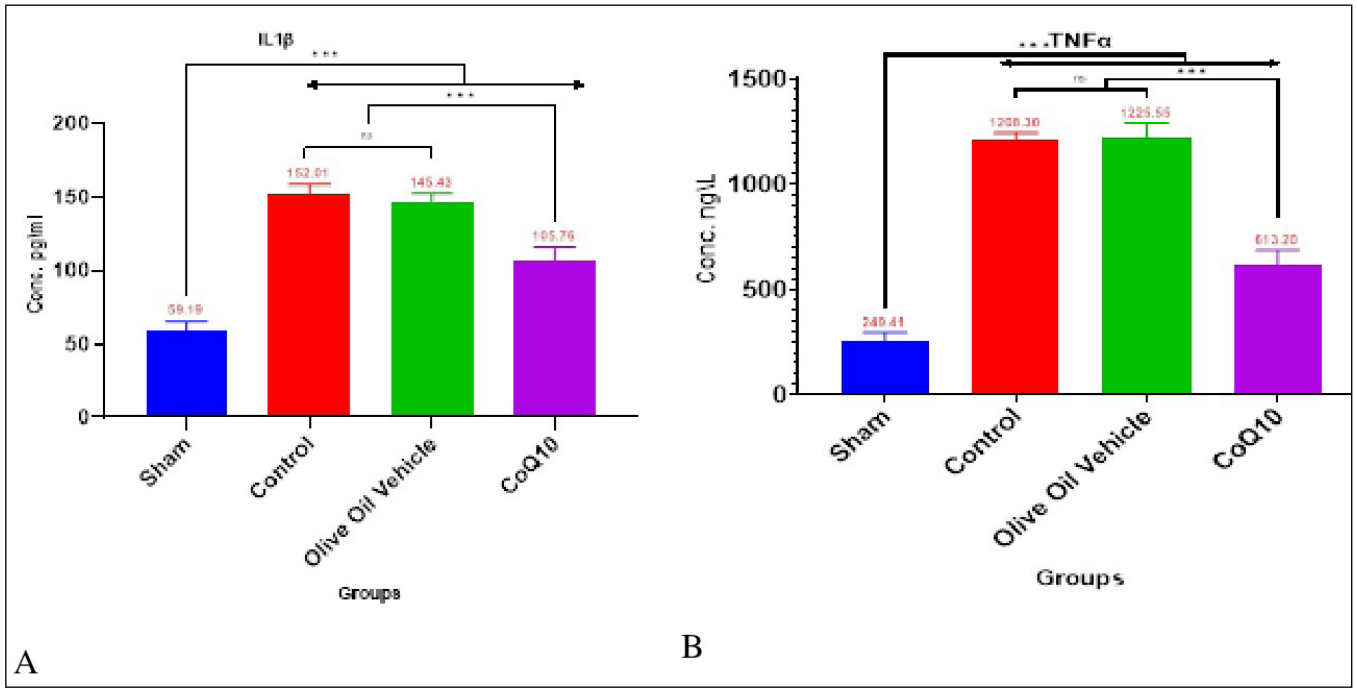

Fig. 2 Error bar chart showing the difference in mean ± SEM values of **(A):** IL1β renal tissue concentration (pg/mL), **(B):** TNFα renal tissue concentration, no. of animals in each group =7, **p<0.01, ***p<0.001.
Source: Own materials

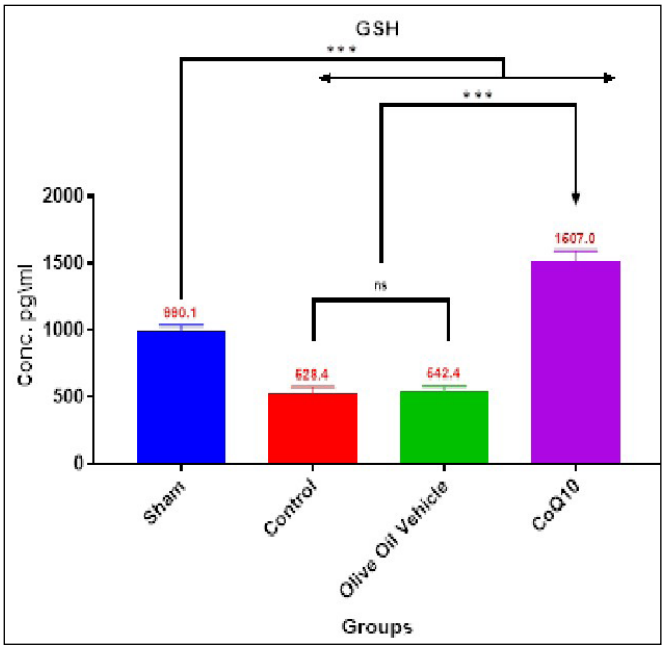

Fig. 3. Error bar chart showing the difference in mean ±SEM values of GSH renal tissue concentration (pg/mL), no. of animals in each group=7, **p<0.01, ***p< 0.001
Source: Own materials

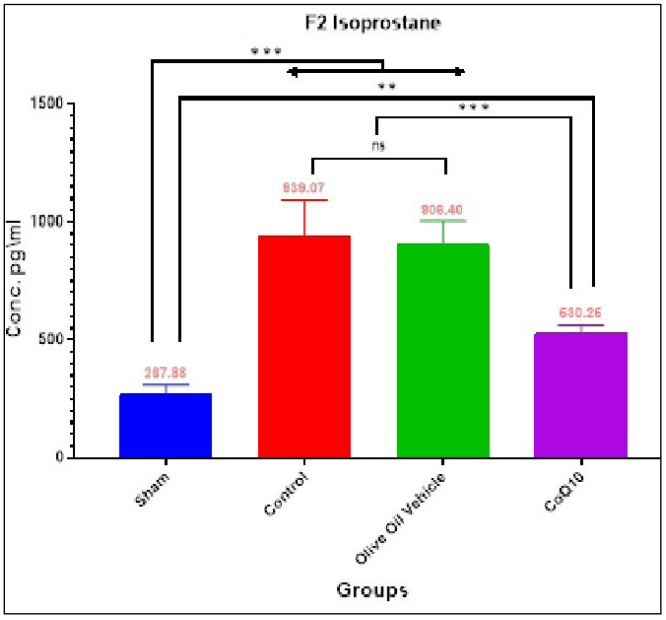

Fig. 4. Error bar chart showing the difference in mean ±SEM values of F2 Isoprostane renal tissue concentration (pg/mL), no. of animals in each group=7, **p<0.01, ***p< 0.001.
Source: Own materials

nique of qRT-PCR. Initially, total RNA was accurately extracted using "Easy-spin™ (DNA free) total RNA extraction Kit". This high-quality total RNA was then expertly reverse-transcribed into cDNA with the help of "AddScript cDNA Synthesis Kit". For the quantitative real-time PCR, we employed the robust GoTaq® RT-qPCR System ensuring the most reliable results. According

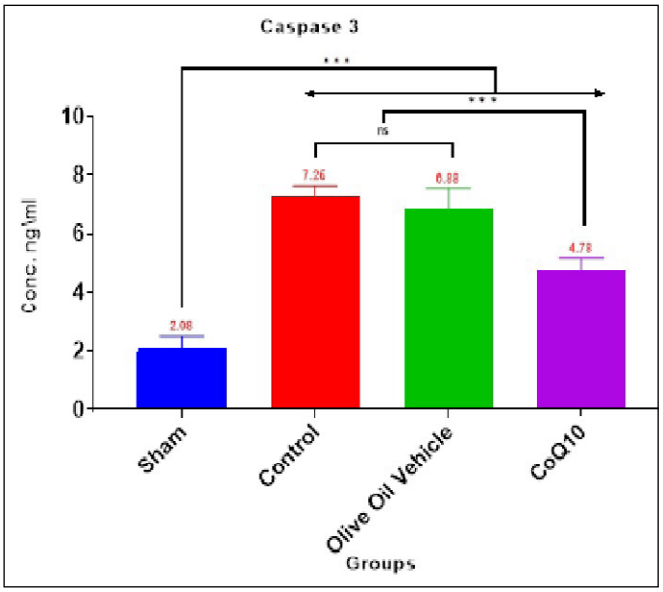

Fig 5. A comparison of Caspase-3 among study groups
**p<0.01, ***p<0.001.
Source: Own materials

to the instruction of GoTaq® RT-qPCR System, Hot-start activation was performed at 95°C for 5 min for 1 cycle, followed by 40 cycles of 10 s of denaturation at 95°C, then 40 cycles of 30 s at 60°C of annealing and 40 cycles of 30 s of extension at 72°C and finally one cycle of 2 min of dissociation at 72°C and specific primers: Notch1 for: CACCCATGACCACTACCCAGTT, Notch-1 rev: CCTCGGACCAATCAGAGATGTT, Jagged1 for: AACTGGTACCGGTGCGAA , Jagged-1 rev: TGATGCAAGATCTCCCTGAAAC [25] and GAPDH for: ATGACTCTACCCACGGCAAG, GAPDH rev. :CTGGAAGATGGTGATGGGTT [26].

STATISTICAL ANALYSIS

To perform the statistical analysis of current study Graph Pad Prism version 8 software was used. Parametric variables were tested using the one-way ANOVA test with multiple comparisons between groups being made by selected Post Hoc test.

RESULTS

COQ10 TREATMENT REDUCES KIM-1 LEVEL IN RAT RENAL TISSUE AFTER RENAL I/R:

KIM-1 renal tissue level was significantly ($p < 0.001$) elevated after renal ischemia /reperfusion (renal I/R) in comparison with sham group. Interestingly, this elevation was attenuated by COQ10 pretreatment in a dose of (10 mg/kg) i.p., however, COQ10 treatment group showed significant ($p < 0.001$) difference when compared to sham group (Fig. 1).

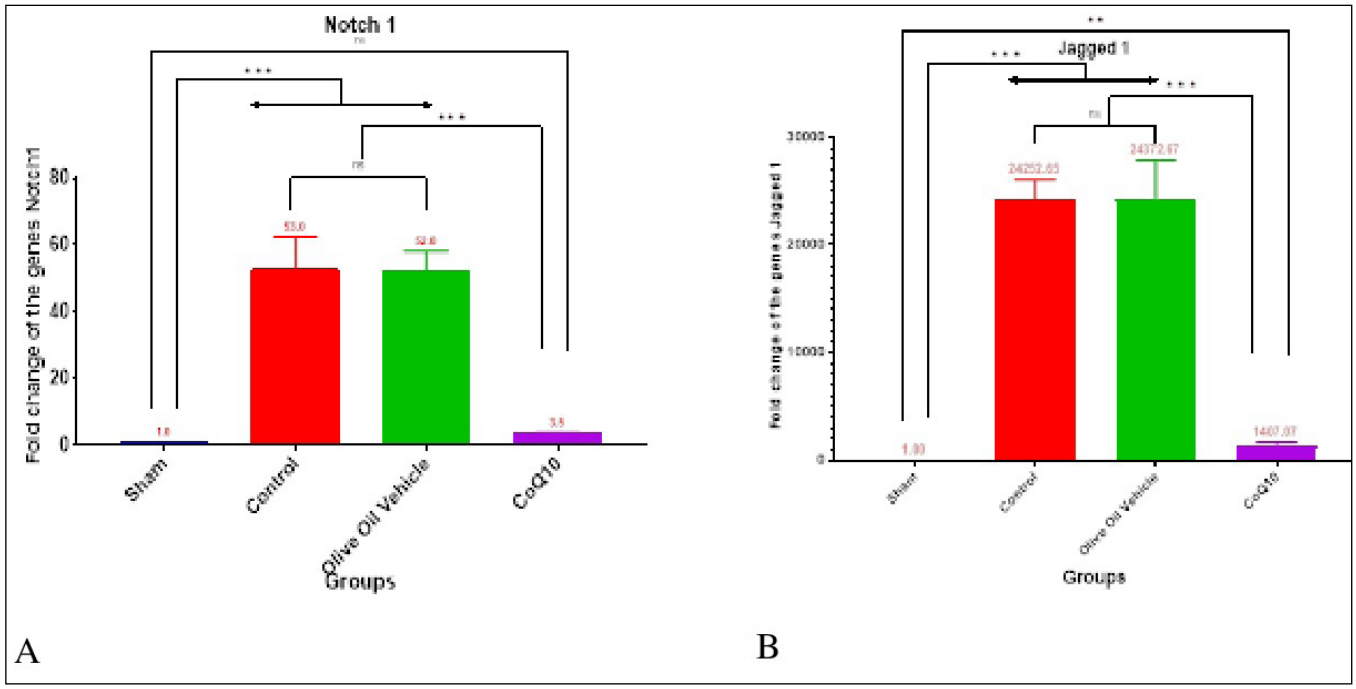

Fig. 6. Error bar chart showing the difference in mean ±SEM values of **A:** Notch-1 mRNA expression level in renal tissue, **B:** Jagged-1 mRNA expression level in renal tissue, no. of animals in each group=7
**p<0.01, ***p<0.001
Source: Own materials

COQ10 TREATMENT REDUCES INFLAMMATORY MARKERS IL-1B AND TNFA IN RAT RENAL TISSUE AFTER RENAL I/R

After renal I/R the renal tissue concentration of both IL-1β and TNFα in rats were significantly (p< 0.001) elevated, COQ10 pretreatment in a dose of (10 mg/kg) i.p. Significantly (p< 0.001) ameliorated the levels of both markers, however, COQ10 treatment group was still significantly (p < 0.001) elevated when compared to sham group (Fig. 2A-B).

COQ10 TREATMENT AMELIORATES GSH LEVELS IN RATS' RENAL TISSUE AFTER RENAL I/R:

Notably, I/R significantly (p< 0.001) reduced GSH level in rat renal tissue relative to sham group. COQ10 pretreatment in a dose of (10 mg/kg) i.p. caused considerable (p< 0.001) elevation in GSH renal tissue concentration in comparison with control group (Fig. 3).

COQ10 TREATMENT REDUCES F2 ISOPROSTANE LEVELS IN RATS' RENAL TISSUE AFTER RENAL I/R

Based on the results of ANOVA as shown in figure 4, the oxidative marker F2 Isoprostane renal tissue concentration was significantly (p<0.001) lower in sham group when compared to control group. However, CoQ10 treatment group was significantly (p<0.001) lower than control group, but it was still significantly (p<0.001) higher, than sham group (Fig. 4).

COQ10 TREATMENT REDUCES CASPASE-3 LEVELS IN RATS' RENAL TISSUE AFTER RENAL I/R

As indicated in figure 5, renal I/R significantly (p<0.001) increased caspase-3 renal tissue concentration while COQ10 pretreatment in a dose of 10 mg/kg i.p. significantly (p<0.001) attenuated this increase, but it was still significantly (p<0.001) higher than sham group (Fig 5).

COQ10 TREATMENT ATTENUATES NOTCH-1 AND JAGGED-1 MRNA EXPRESSION IN RAT'S RENAL TISSUE AFTER RENAL I/R

Both Notch-1 and its ligand Jagged-1 mRNA expression were significantly (p<0.001) elevated in rats renal tissue after I/R, this elevation was significantly (p<0.001) attenuated by COQ10 pretreatment in a dose of 10mg/kg i.p. (Fig. 6A-B).

DISCUSSION

Many molecular pathways have been suggested to mediate the pathogenic processes which ultimately lead to cellular damage that is associated with renal IRI.

In addition, Fundamental research has revealed several targets that could potentially slow the advancement of kidney disease. However, only a limited number of these encouraging findings have been successfully replicated in clinical trials, and they still do not offer a significant alternative to dialysis or transplantation. So, there is an urgent requirement to further elucidate the development of molecular mechanisms underlying renal I/R injury as well as exploring new therapeutic targets that can mitigate the outcomes of this pathologic condition. In this study, we evaluated the nephroprotective effects of COQ10 against renal IRI and the relation of Notch signalling pathway in mediating these effects. The current study revealed significant elevation in renal tissue level of KIM-1 after renal I/R Because KIM-1 is not found in healthy renal tissue and is exclusively expressed in damaged proximal tubules, it serves as a highly sensitive, specific, and precise early indicator of renal tubular injury [27], which confirms the success of IRI model of this study. COQ10 pretreatment caused considerable reduction in KIM-1 renal tissue level in comparison with control group and olive oil vehicle groups which suggests that COQ10 confers protection against renal tissue damage. The decline in KIM-1 level with COQ10 treatment could be due to the antioxidative effects of COQ10 since it can lower the expression of reactive oxygen species (ROS) in damaged cells, decrease mitochondrial depolarization, and improve mitochondrial ATP levels, also, it can boost mitochondrial function, improve cell survival, and decrease apoptosis [28]. IL1β and TNFα were both significantly elevated in control group comparison with sham which confirms the role of the inflammatory response in renal ischemia/reperfusion (I/R) injury. It has become evident that a significant portion of the damage that occurs after renal I/R is due to mitochondrial oxidative stress and the presence of reactive oxygen species (ROS) during reperfusion. These ROS, which include superoxide, peroxynitrite, and hydrogen peroxide (H2O20) trigger the activation of inflammatory cells which result in the release of interleukins (ILs), tumor necrosis factor (TNF-α), and various other inflammatory mediators [29-30] COQ10 pretreatment considerably attenuated the increase in both IL1β and TNFα that is induced by renal I/R. This effect of CoQ10 can be linked to its strong anti-oxidative properties which can block the activation of the NF-B signaling pathway that triggers the expression of the TNF- α and iNOS genes [31]. Glutathione (GSH) which is an intracellular antioxidant has been demonstrated to quickly recognize and interact specifically with hydroxyl radicals (OH•), which are the most reactive types of reactive oxygen species (ROS). Additionally, GSH detoxifies hydrogen peroxide (H_2O_2) and lipid peroxides through the activity of GSH-Px, safeguarding cell membranes from lipid oxidation [32]. The present study showed significant reduction in GSH levels after renal I/R. This reflects the depletion of the tissue antioxidative capacity due the production of huge amounts of ROS during the reperfusion phase as a result of the defect in mitochondrial electron transport chain [33]. The present study comes in line with another study conducted to evaluate the nephroprotective effects of curcumin in renal IRI which have shown the reduction in GSH level in serum after clipping the left renal artery for 45min and then reperfusion for 24h [34]. COQ10 pretreatment on the other hand caused significant elevation in GSH level which affirms its antioxidant properties apart from its role in the respiratory chain. Another marker of oxidative stress was evaluated in this study which is F2-isoprostane. it is generated through a non-enzymatic process, resulting from the powerful peroxidation of arachidonic acid driven by free radicals. In the present study renal tissue concentration of F2-isoprostane was considerably elevated after renal I/R. this elevation was significantly ameliorated by COQ10 pretreatment. This effect could be attributed to the fact that CoQ10 is not only a strong antioxidant but also plays a crucial role in preventing the formation of reactive oxygen species. It helps to eliminate lipid peroxidation byproducts during reactions with free radicals, reduces excessive nitric oxide production, and protects tissues from nitrative stress [35]. Apoptosis, often referred to as programmed cell death, plays an important role in renal ischemia-reperfusion injury (RIRI). Caspase-3 is considered one of the key proteins involved in the apoptotic process which is activated in the final common pathway of both intrinsic and extrinsic apoptosis [36]. our study demonstrated significant increase in caspase-3 renal tissue concentration after renal I/R which come in line with other studies that showed caspase-3 to be upregulated in the early stages of renal I/R injury which strengthen the evidence that apoptosis is activated and might play a role in the pathogenesis of renal I/R injury [37]. COQ10 pretreatment on the other hand resulted in considerable reduction of caspase-3 renal tissue levels confirming the anti-apoptotic effects of COQ10 [19]. To investigate the relation between COQ10 nephroprotective effects and Notch-1 molecular pathway, we evaluated ligand Jagged-1 mRNA expression and Notch-1 in all study groups. Jagged-1 mRNA expression and Notch-1 were noticeably elevated after renal I/R. Notch signaling plays an essential role in the development and segmentation of nephrons and has been associated with kidney disorders [38]. Studies in mouse models have indicated that in adult mice, Notch signaling can be detrimental, resulting in abnormal podocyte differentiation, cell death,

and eventually kidney failure [39]. The upregulation of Notch-1 and its ligand along with the other inflammatory, oxidative and apoptotic parameters in the present study might provide further evidence about the detrimental effects of Notch-1 signaling pathway in renal I/R injury. Interestingly COQ10 pretreatment caused significant amelioration of Notch-1 and Jagged-1 mRNA expression in renal tissues after renal I/R. The present study considered to be novel for assessment the effect of COQ10 pretreatment on Notch-1 and its ligand Jagged-1 m RNA expression after renal I/R in rats showing possible correlation between COQ10 nephroprotective effects and Notch-1 regulation in renal I/R injury. A number of previous studies have shown cross talks between Notch-1 signaling and oxidative stress pathways [40]. By reducing oxidative harm, CoQ10 may help stabilize Notch-1 signaling and avert its disruption in addition to enhancing mitochondrial performance with CoQ10 supplementation could aid in maintaining healthy Notch-1 signaling, especially in high-energy-demand tissues like the kidney.

CONCLUSIONS

The findings of the present study may add further evidence about the role of inflammation, oxidative stress and apoptosis in the pathogenesis of renal I/R injury suggesting the involvement of Notch-1 signaling pathway in mediating these effects. COQ10 may have protective effects in renal ischemia reperfusion injury due to its anti-inflammatory, anti-oxidative and anti-apoptotic effects. In addition, COQ10 protective effects were associated with downregulation of Notch-1 and its ligand Jagged-1.

REFERENCES

1. Agarwal A, Dong Z, Harris R, Murray P, et al. Acute Dialysis Quality Initiative XIII Working Group. Cellular and molecular mechanisms of AKI. J Am Soc Nephrol. 2016 May;27(5):1288-99. doi: 10.1681/ASN.2015070740.
2. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant. 2011 Nov;11(11):2279-96. doi: 10.1111/j.1600-6143.2011.03754.x. DOI
3. Zhu Y, Zhao K, Wang L, Lu T, et al. Erythropoietin preconditioning mobilizes endothelial progenitor cells to attenuate nephron-sparing surgery-induced ischemia-reperfusion injury. Transplant Proc. 2020 Dec;52(10):2955-2963. doi: 10.1016/j.transproceed.2020.05.008. DOI
4. Zhao H, Alam A, Soo AP, George AJ, Ma D. Ischemia-reperfusion injury reduces long term renal graft survival: mechanism and beyond. EBioMedicine. 2018 Feb;28:31-42. doi: 10.1016/j.ebiom.2018.01.025. DOI
5. Sato C, Zhao G, Xenia G. Ilagan M. An overview of notch signaling in adult tissue renewal and maintenance. Curr Alzheimer Res. 2012 Feb; 9(2):227-40. doi: 10.2174/156720512799361600. DOI
6. Sörensen-Zender I, Rong S, Susnik N, Zender S, et al. Renal tubular Notch signaling triggers a prosenescent state after acute kidney injury. Am J Physiol Renal Physiol. 2014 Apr;306(8):F907-15. doi: 10.1152/ajprenal.00030.2014. DOI
7. Radtke F, Fasnacht N, MacDonald HR. Notch signaling in the immune system. Immunity. 2010 Jan; 32(1): 14-27. doi: 10.1016/j.immuni.2010.01.004. DOI
8. Bray SJ. Notch signaling in context. Nature Rev Molec Cell Biol. 2016 Nov;17(11):722-35. doi: 10.1038/nrm.2016.94. DOI
9. Gallenstein N, Tichy L, Weigand MA, Schenz J. Notch signaling in acute inflammation and sepsis. Int J Molec Sci. 2023 Feb;24(4):3458. doi: 10.3390/ijms24043458. DOI
10. Zhou B, Lin W, Long Y, Yang Y, et al. Notch signaling pathway: architecture, disease, and therapeutics. Signal Transduct Target Ther. 2022 Mar 24;7(1):95. doi: 10.1038/s41392-022-00934-y. DOI
11. Mangolini M, Götte F, Moore A, Ammon T, et al. Notch2 controls non-autonomous Wnt-signalling in chronic lymphocytic leukemia. Nat Commun. 2018 Sep 21;9(1):3839. doi: 10.1038/s41467-018-06069-5. DOI
12. Chen LJ, Zhang NN, Zhou CX, Yang ZX, Li YR, Zhang T, et al. Gm364 coordinates MIB2/DLL3/Notch2 to regulate female fertility through AKT activation. Cell Death Differ. 2022 Feb;29(2):366-380. doi: 10.1038/s41418-021-00861-5. DOI
13. Little MH, Kairath P. Does renal repair recapitulate kidney development? J Am Soc Nephrol. 2017 Jan;28(1):34-46. doi: 10.1681/ASN.2016070748. DOI
14. Huang R, Zhou Q, Veeraragoo P, Yu H, Xiao Z. Notch2/Hes-1 pathway plays an important role in renal ischemia and reperfusion injury-associated inflammation and apoptosis and the γ-secretase inhibitor DAPT has a nephroprotective effect. Ren Fail. 2011 Mar; 33(2): 207-216. doi: 10.3109/0886022X.2011.553979. DOI
15. Nattagh-Eshtivani E, Dahri M, Hashemilar M, Tarighat-Esfanjani A. The effect of Coenzyme Q10 supplementation on serum levels of lactate, pyruvate, matrix metalloproteinase 9 and nitric oxide in women with migraine. A double blind, placebo, controlled randomized clinical trial. Eur J Integr Med. 2018 Aug; 21: 70-6. doi: 10.1016/j.eujim.2018.06.009 DOI

16. Akbel E, Kucukkurt I, Ince S, Demirel HH, et al. Investigation of protective effect of resveratrol and coenzyme Q10 against cyclophosphamide-induced lipid peroxidation, oxidative stress and DNA damage in rats. Toxicol Res. 2024 Feb; 13(1): tfad123. doi:10.1093/toxres/tfad123. DOI
17. Giorgi C, Marchi S, Simoes IC, Ren Z, et al. Mitochondria and reactive oxygen species in aging and age-related diseases. Int Rev Cell Molec Biol. 2018 Jan; 340: 209-344. doi: 10.1016/bs.ircmb.2018.05.006. DOI
18. Sharma A, Patnai P, Mehta N, Dalwadi P. Effect of coenzyme Q10 alone and it's combination with pentoxifylline in cisplatin-induced nephrotoxicity in rats. J Pharm Sci Biosci Res. 2016;6(1):790-800.
19. Akbulut A, Bilge Keseroglu B, Koca G, Nedim Yuceturk C, Cem Ozgur B, Surer H, et al. Scintigraphic evaluation of renoprotective effects of coenzyme Q10 in a rat renal ischemia-reperfusion injury. Nuc Med Commun. 2019 Oct; 40(10):1011-21. doi: 10.1097/MNM.0000000000001070. DOI
20. Liu Z, Liu X, Yang Q, Yu L, Chang Y, Qu M. Neutrophil membrane-enveloped nanoparticles for the amelioration of renal ischemia-reperfusion injury in mice. Acta Biomater. 2020 Mar;104:158-66. doi:10.1016/j.actbio.2020.01.018. DOI
21. Ozer EK, Goktas MT, Kilinc I, Pehlivan S, Bariskaner H, Ugurluoglu C, et al. Coenzyme Q10 improves the survival, mesenteric perfusion, organs and vessel functions in septic rats. Biomed Pharmacother. 2017 Jul; 91: 912-9. doi: 10.1016/j.biopha.2017.05.017. DOI
22. Khanegheini A, Khani M, Zarrabian S, Yousefzadeh-Chabok S, Taleghani BK, Haghparast A. Cannabidiol enhanced the development of sensitization to the expression of methamphetamine-induced conditioned place preference in male rats. J Psychiatr Res. 2021;137:260-265. doi: 10.1016/j.jpsychires.2021.02.045.
23. Wang J, Xiong M, Fan Y, Liu C, et al. Mecp2 protects kidney from ischemia-reperfusion injury through transcriptional repressing IL-6/STAT3 signaling. Theranostics. 2022 May; 12(8): 3896. doi: 10.7150/thno.72515. DOI
24. Alnfakh ZA, Al-Mudhafar DH, Al-Nafakh RT, Jasim AE, Hadi NR. The anti-inflammatory and antioxidant effects of Montelukast on lung sepsis in adult mice. J Med Life. 2022 Jun;15(6):819-827. doi: 10.25122/jml-2021-0269. DOI
25. Köhler C, Bell AW, Bowen WC, Monga SP, Fleig W, Michalopoulos GK. Expression of Notch-1 and its ligand Jagged-1 in rat liver during liver regeneration. Hepatology. 2004 Apr;39(4):1056-65. doi: 10.1002/hep.20156. DOI
26. Kunst S, Wolloscheck T, Hölter P, Wengert A, Grether M, Sticht C, et al. Transcriptional analysis of rat photoreceptor cells reveals daily regulation of genes important for visual signaling and light damage susceptibility. J Neurochem. 2013 Mar;124(6):757-69. doi: 10.1111/jnc.12089. DOI
27. Yan BO, Min SJ, Xu B, Zhang C, et al. The protective effects of exogenous spermine on renal ischemia-reperfusion injury in rats. Transl Androl Urol. 2021 May;10(5):2051-2066. doi: 10.21037/tau-21-280. DOI
28. Schijvens AM, van de Kar NC, Bootsma-Robroeks CM, Cornelissen EA, van den Heuvel LP, Schreuder MF. Mitochondrial disease and the kidney with a special focus on CoQ10 deficiency. Kidney Int Rep. 2020 Dec; 5(12): 2146-59. doi: 10.1016/j.ekir.2020.09.044. DOI
29. Alaasam ER, Janabi AM, Al-Buthabhak KM, Almudhafar RH, et al. Nephroprotective role of resveratrol in renal ischemia-reperfusion injury: a preclinical study in Sprague-Dawley rats. BMC Pharmacol Toxicol. 2024 Oct;25(1):82. doi: 10.1186/s40360-024-00809-8. DOI
30. Gu L, Tao Y, Chen C, Ye Y, Xiong X, Sun Y. Initiation of the inflammatory response after renal ischemia/reperfusion injury during renal transplantation. Int Urol Nephrol. 2018 Nov;50:2027-35. doi: 10.1007/s11255-018-1918-6. DOI
31. Abiri B, Vafa M. Impact of coenzyme Q10 on inflammatory biomarkers and its role in future therapeutic strategies. Clin Nutr ESPEN. 2021 Jun;43:25-30. doi: 10.1016/j.clnesp.2021.04.005. DOI
32. Ali HR, Albakaa RN. Potential role of selenium to ameliorate doxorubicin induced cardiotoxicity in male rats. J Med Chem Sci. 2023;6(7):1498-1505. doi:10.26655/JMCHEMSCI.2023.7.3 DOI
33. Chouchani ET, Pell VR, James AM, Work LM, Saeb-Parsy K, Frezza C, et al. A unifying mechanism for mitochondrial superoxide production during ischemia-reperfusion injury. Cell Metab. 2016 Feb 9;23(2):254-63. doi: 10.1016/j.cmet.2015.12.009. DOI
34. Cui X, Lin L, Sun X, Wang L, Shen R. Curcumin protects against renal ischemia/reperfusion injury by regulating oxidative stress and inflammatory response. Evid Based Complement Alternat Med. 2021; 2021(1): 8490772. doi: 10.1155/2021/8490772. DOI
35. Peerapanyasut W, Thamprasert K, Wongmekiat O. Ubiquinol supplementation protects against renal ischemia and reperfusion injury in rats. Free Rad Res. 2014 Feb;48(2):180-9. doi: 10.3109/10715762.2013.858148. DOI
36. Yang B, Lan S, Dieudé M, Sabo-Vatasescu JPet al. Caspase-3 is a pivotal regulator of microvascular rarefaction and renal fibrosis after ischemia-reperfusion injury J Am Soc Nephrol. 2018 Jul;29(7):1900-1916. doi: 10.1681/ASN.2017050581. DOI
37. Jallawee HQ, Janabi AM. Potential nephroprotective effect of dapagliflozin against renal ischemia reperfusion injury in rats via activation of autophagy pathway and inhibition of inflammation, oxidative stress and apoptosis. South East Eur J Public Health. 2024;24:488-500. doi: 10.70135/seejph.vi.1009. DOI
38. Mukherjee M, Fogarty E, Janga M, Surendran K. Notch signaling in kidney development, maintenance, and disease. Biomolecules. 2019 Nov;9(11):692. doi: 10.3390/biom9110692. DOI
39. Edeling M, Ragi G, Huang S, Pavenstädt H, Susztak K. Developmental signalling pathways in renal fibrosis: the roles of Notch, Wnt and Hedgehog. Nat Rev Nephrol. 2016 Jul;12(7):426-39. doi: 10.1038/nrneph.2016.54. DOI

40. Luo G, Wang R, Zhou H, Liu X. ALDOA protects cardiomyocytes against H/R-induced apoptosis and oxidative stress by regulating the VEGF/Notch 1/Jagged 1 pathway. Molecular and cellular biochemistry. 2021 Feb;476(2):775-83. Mol Cell Biochem. 2021 Feb;476(2):775-783. doi: 10.1007/s11010-020-03943-z. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Manar H. Mohammed
Department of Basic Sciences, Faculty of Dentistry,
University of Kufa
Al Najaf Al-Ashraf, Iraq
e-mail: manarh.radhi@uokufa.edu.iq

ORCID AND CONTRIBUTIONSHIP

Manar H. Mohammed: 0000-0002-6598-3736 B C D E
Fadhil A. Rizij: 0000-0002-2791-5353 A F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 12.05.2025
ACCEPTED: 29.08.2025