Protection of Coenzyme Q-10 Against Contrast-induced Acute Kidney Injury in Diabetic Rats

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Research

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Abstract

Background: Diabetes Mellitus (DM) is an important risk factor for Contrast-induced acute kidney injury (CI-AKI). DM and CI-AKI share oxidative damage and inflammation mechanisms that induction of protective and cellular adaptation enzymes as coenzyme Q-10 (COQ-10). The aim of this study was to investigate the therapeutic potential of COQ-10 in renal function, renal hemodynamics, oxidative profile and renal histology in diabetic rats submitted to the CI-AKI model.

Methods: Wistar rats, male, randomized into four groups: Citrate- control animals, received citrate buffer (streptozotocin vehicle, 0.4 ml); DM- animals that received streptozotocin (60 mg/kg); DM+IC: DM animals, treated with iodinated contrast (IC, 6 ml/kg); DM+IC+COQ-10: DM animals treated with COQ-10 (10 mg/kg) and that received with IC (6 ml/kg). The protocols lasted 4 weeks. Were evaluated the renal function by inulin clearance and serum creatinine, renal hemodynamics by renal blood flow (RBF) and renal vascular resistance (RVR), markers of oxidative stress such as urinary peroxides and nitrate, lipid peroxidation, thiols in renal tissue and renal histological analysis.

Results: DM animals showed reduced renal function which was reflected with an increase of serum creatinine and significant reduced of inulin clearance, as well as a reduction on RBF, increased RVR and redox imbalance with a higher urinary peroxides, nitrate lipid peroxidation levels and depletion of thiols in renal tissue. IC treatment exacerbated theses changes in DM + IC. COQ-10 administration ameliorates renal function, prevented hemodynamic changes, neutralize oxidative damage and progression of the histologic damage in the DM+IC+COQ-10 group.

Conclusion: This study is the first that demonstrated a renoprotection of COQ-10 in experimental model of risk factor of DM for CI-AKI. COQ-10 presented an antioxidant effect on the CI-AKI in diabetic rats, by improving function and renal hemodynamics, preserving morphology and reducing oxidative stress.

Background

Contrast-induced acute kidney injury (CI-AKI) has been the third most common cause of acute renal injury in hospitalized patients become a significant source of hospital morbidity and mortality, length of hospitalization, and healthcare costs [1, 2]. Diabetes Mellitus (DM) is one of the world’s most common chronic metabolic disorders and it is associated with loss of kidney function, increasing the risk of chronic kidney disease (CKD) [3, 4]. DM is considered an important risk factor for CI-AKI. Almost 28,2% of patients that developed CI-AKI was associated with preprocedural hyperglycemia and 26,6% was related have severe level of glomerular filtration rate [5, 6].

Chronic hyperglycemia contributes to increase endothelin and angiotensin levels, causing intrarenal vasoconstriction, change of intrarenal blood flow, reducing pH and oxygen delivery, increasing reactive oxygen species (ROS) and Inflammatory cytokines [3, 7]. The increase in the ROS in DM may be associated the development of CI-AKI, whose the pathogenesis is due of endothelial dysfunction, defective nitrovasodilation, cellular toxicity from the contrast media and tubular apoptosis resulting in
hypoxia [2, 8]. Therefore, DM and CI-AKI share oxidative damage and inflammation mechanisms that favors oxidative stress and cytokines liberation [2, 3].

Oxidative stress is defined with an imbalance between the ROS and antioxidant defenses, and is responsible by increase of formation mutagenic compounds, atherogenic activity, and inflammatory processes [9, 10].

Coenzyme Q-10 (COQ-10), a protein of the mitochondrial respiratory and has been highlighted by plays an antioxidant and anti-inflammation [4, 11]. As an intracellular antioxidant, COQ-10 is able to protects phospholipids and proteins of membrane from oxidative damage and also demonstrates anti-inflammatory effect participating in the modulation of inflammatory cytokines and transcription factors [12, 13]. COQ-10 induction has already evidenced renoprotective activity in an animal models of diabetic nephropathy and cisplatin nephrotoxicity [14, 15].

Thus, the aim of this study was to investigate the therapeutic potential of COQ-10 in renal function, renal hemodynamics, oxidative profile and renal histology in diabetic rats submitted to the CI-AKI model.

Methods

Animals

Adult male Wistar rats (weighing 250–290 g) were used. The animals obtained from the Institute of Biomedical Sciences at the University of Sao Paulo, were housed at Experimental Laboratory of Animal Models (LEMA) at the School of Nursing, University of Sao Paulo, in a room at a controlled temperature (25ºC/77 ºF) on alternating light/dark cycles, and had free access to water and rat chow. The study was approved by the Ethical Committee of Experimental Animals, University of Sao Paulo (CEEA – protocol nº 055/15).

Streptozotocin-induced diabetes mellitus model

The animals received 60 mg/kg Streptozotocin (STZ, Chemical Company, USA), diluted in 0.4 ml citrate buffer (0.1 mol/L; pH 4.5), intravenous (i.v.) tail, for DM type 1 induction. Blood glucose levels were measured 48 h after to confirm hyperglycemia (Accu-Chek, Roche, USA) and considered diabetic animals that showed blood glucose level higher than 250 mg/dL [16].

Iodinated contrast induced CI-AKI model

The animals received 6 mL/kg of iodinated contrast (IC, meglumine ioxithalamate and sodium) intraperitoneal (i.p.), single dose [17].

Coenzyme Q-10 administration

Animals submitted to administration of 10mg/kg of COQ-10 (Sigma Chemical Company, USA) i.p., dissolved in a solution of 1% of Tween 80, for 6 days [18].
Experimental groups

- Citrate (n = 7): control group of chronic DM model, rats that received 0.5 mL of citrate buffer (STZ vehicle), i.v. tail, single dose on 1th day;
- Diabetes Mellitus (DM, n = 7): rats receiving 60 mg/kg of STZ diluted in 0.5 mL citrate buffer i.v. tail, single dose on 1th day;
- Diabetes Mellitus + iodinated contrast (DM + IC, n = 7): rats DM that received 6 mL/Kg of IC intraperitoneal (i.p.), single dose on 26th day.
- Diabetes Mellitus + iodinated contrast + CoenzymeQ-10 (DM + IC + COQ-10, n = 7): DM rats receiving received COQ-10, i.p., diluted in 80% Tween, 1%. Treatment with COQ-10 was started on the 22th day of the experimental protocol. There were four preconditioning days, followed by a dose administered on the same day as CI administration and the last dose on the following day.

Procedures and timing of experimental protocols

All protocols of experimental groups lasted four week. Animals were allocated in individual metabolic cages on 27th day, for 24 hours, for collection of urine and determination of urinary flow. On the 28th day of the protocol, the rats were anesthetized with 10 mg/kg xylazine and 90 mg/kg ketamine i.p., and submitted surgical procedure for renal function and hemodynamics measurement. After, a blood sample was collected through a puncture of the abdominal aorta. Finally, animals were submitted euthanasia according to guidelines for animal experimentation and removal of kidneys for thiols assay and histological analysis.

Renal Function Measurement

*Inulin clearance (ml/min)*: renal function was evaluated based on inulin clearance. Inulin was injected in right jugular vein by catheter (polyethylene tube PE-60), as a loading dose (100 mg/kg), followed by a continuous infusion of 0.04 ml/min. After a 30 min equilibration period, three urine collections were made through the bladder catheter and two blood samples were then obtained at the carotid catheter. The serum and urinary inulin were measured using the Anthrone method [19, 20].

*Serum creatinine (Cr) (mg/dl)*: was measured using the Jaffé method. The results were expressed as mg/dl [21].

Renal Hemodynamic Measurement

*Renal blood flow*: was measured by an ultrasonic flowmeter (T402, Transonic Systems Inc., USA) placed around renal artery isolated [19].

*Renal vascular resistance*: Mean arterial blood pressure (MAP) by catheter inserted into the left carotid (polyethylene tube PE-60) and renal blood flow (RBF) were measured and the renal vascular resistance (RVR) was calculated with the formula: \( RVR = \frac{MAP}{RBF} \) [19].

Oxidative profile
Urinary peroxides: Were determined by method of ferrous oxidation of xylenol orange version 2 (FOX-2). Results were expressed as nmol/g urinary Cr [22].

Urinary nitrate: Was measured using the Griess method. Results were expressed as nmol/g urinary Cr [23].

Urinary thiobarbituric acid reactive substances (TBARS): Urinary TBARS is an indirect measure of lipid peroxidation. This assay is based on the reaction of urine samples with 17.5% trichloroacetic acid (TCA) and 0.6% thiobarbituric acid at 95°C for 20 min, after cooling, 70% TCA is added and incubated for 20 min. The amount of TBARS was expressed as nmol / g urinary Cr [24].

Soluble non-protein thiols in renal tissue: The thiol antioxidant assay was by Ellman method. The amount of soluble thiols was corrected for total protein measured by Bradford method and results was expressed as nmol / mg total protein [25, 26].

Urinary Cr by Jaffé method was used to correct oxidative parameters [21].

Histological Analysis

Tubulointerstitial damage: kidney tissue was sectioned, stained with hematoxylin and eosin, and examined under light microscopy (magnification ×400). Tubulointerstitial damage was examined for extent of cortical and outer medullae involvement of tubule interstitial damage of tubules that displayed: tubular epithelial swelling, vacuolar degeneration, necrosis, and desquamation, presence of an inflammatory cell infiltrate, tubular lumen dilatation or tubular atrophy [19].

Statistical Analysis

The results are reported as the mean ± standard error (SEM). Used the analysis of variance by One Way ANOVA and post test Newman-Keuls to comparisons of groups. Statistical significance was defined at p < 0.05. All statistical analyses were performed Graph-Pad Prism version-7 for Windows®.

Results

Effect of COQ-10 treatment on renal function

The results show the effect of COQ-10 on renal function after injury is demonstrated in Table 1. Rats submitted to DM showed a significant increase in urinary flow, serum Cr and decrease in inulin clearance. DM + IC group resulted additional elevation in serum Cr and a reduction in inulin clearance compared to the DM group, whereas these parameters were changed by the COQ-10 treatment that significantly decreased serum Cr and improved inulin clearance in the DM + IC + COQ-10 group.
Table 1
Renal function.

| Groups          | n  | Urinary flow (ml/min) | Serum Creatinine (mg/dl) | Inulin Clearance (ml/min) |
|-----------------|----|-----------------------|--------------------------|--------------------------|
| Citrate         | 7  | 0.011 ± 0.002         | 0.30 ± 0.05              | 0.90 ± 0.26              |
| DM              | 7  | 0.059 ± 0.009 a       | 0.77 ± 0.18 a            | 0.52 ± 0.09 a            |
| DM + IC         | 7  | 0.065 ± 0.008 a       | 1.06 ± 0.17 ab           | 0.16 ± 0.05 ab           |
| DM + IC + COQ-10| 7  | 0.071 ± 0.017 a       | 0.75 ± 0.09 ac           | 0.41 ± 0.06 ac           |

a p < 0.05 vs Citrate; b p < 0.05 vs DM; c p < 0.05 vs DM + IC.

Effect of COQ-10 treatment on hemodynamic parameters

Data illustrate in Table 2 the effect of COQ-10 in renal hemodynamic. Was observed a significant reduction in RVR and elevation in RBF on the DM group, this changes were exacerbated in DM + IC group, whereas, COQ-10 prevented hemodynamic changes. As showed, the treatment with COQ-10 significantly increased RBF and decreased RVR in DM + IC + COQ-10 group.

Table 2
Renal Hemodynamic.

| Groups             | n  | Renal blood flow (ml/min) | Renal vascular resistance (mmHg/ml/min) |
|--------------------|----|---------------------------|----------------------------------------|
| Citrate            | 7  | 7.47 ± 1.38               | 13.71 ± 3.09                           |
| DM                 | 7  | 4.58 ± 0.63 a             | 23.71 ± 6.80 a                         |
| DM + IC            | 7  | 2.84 ± 0.87 ab            | 37.85 ± 8.88 ab                        |
| DM + IC + COQ-10   | 7  | 5.01 ± 0.67 ac            | 20.07 ± 3.22 c                         |

a p < 0.05 vs Citrate; b p < 0.05 vs DM; c p < 0.05 vs DM + IC.

Effects of COQ-10 treatment on oxidative profile

The Table 3 summarize the oxidative profile. DM group show significantly increased oxidative metabolites and reduction antioxidant activities of soluble non-protein thiols in renal tissue. The redox imbalance findings were more pronounced in the diabetic group that was treated with IC, DM + IC, compared to DM. Treatment with COQ-10 reduced oxidative stress demonstrated by decreased urinary
peroxides, nitrite and TBARS excretion in DM + IC + COQ-10 group, furthermore, COQ-10 significantly preserved antioxidant capacity, confirmed by increased of soluble non-protein thiols in renal tissue.

Table 3
Oxidative profile

| Groups                 | n  | Urinary peroxides (nmol/g urinary Cr) | Urinary nitrate (µM/g urinary Cr) | TBARS (nmol/g urinary Cr) | Thiols (nmol/mg total protein) |
|------------------------|----|-------------------------------------|-----------------------------------|---------------------------|-----------------------------|
| Citrate                | 7  | 1.31 ± 0.83                         | 27.10 ± 4.96                      | 0.25 ± 0.14               | 24.80 ± 5.60                |
| DM                     | 7  | 6.95 ± 0.89                      $^a$| 54.15 ± 11.59                      | 12.91 ± 2.79 $^a$        | 14.82 ± 2.16 $^a$          |
| DM + IC                | 7  | 17.31 ± 4.47                      $^{ab}$| 75.32 ± 9.65                      | 22.84 ± 5.16 $^{ab}$    | 9.28 ± 1.04 $^{ab}$        |
| DM + IC + COQ-10       | 7  | 4.09 ± 0.87                      $^c$| 56.55 ± 14.87                      | 15.74 ± 3.87 $^{abc}$   | 14.21 ± 2.12 $^{ac}$       |

$^a$ p < 0.05 vs Citrate; $^b$ p < 0.05 vs DM; $^c$ p < 0.05 vs DM + IC.

Histological analysis

As shown in Table 4 and Fig. 1, all groups showed slight changes with impairment of less than 5% of the tissue focal areas. Histological changes in DM group was significantly higher compared to the citrate group. Figure 1B shows DM resulted in a discrete edema and increased interstitial area. The DM + IC group showed a significant increase in the tubulointerstitial lesion area compared to the DM group. After IC (Fig. 1C), kidneys presented tubulointerstitial injury characterized by edema, flattening of tubular cells and diffuse inflammatory interstitial infiltration (Fig. 1B). Treatment with COQ-10 show significantly reduced in extension area of the tubulointerstitial lesion compared to DM + IC as illustrate images in Fig. 1D of renal histological analysis.

Table 4
Tubulointerstitial damage.

| Groups                  | n  | Tubulointerstitial damage (%) |
|-------------------------|----|-------------------------------|
| Citrate                 | 5  | 0.05 ± 0.02                   |
| DM                      | 5  | 0.27 ± 0.09 $^a$              |
| DM + IC                 | 5  | 0.45 ± 0.13 $^{ab}$           |
| DM + IC + COQ-10        | 5  | 0.29 ± 0.09 $^{ac}$           |

$^a$ p < 0.05 vs Citrate; $^b$ p < 0.05 vs DM; $^c$ p < 0.05 vs DM + IC.
Discussion

The present study evaluated the participation of oxidative stress in the pathophysiology of CI-AKI with DM as a risk factor and investigated the role of COQ-10 as a possible treatment for this pathology. Oxidative stress and inflammation status are correlated in the prognosis of CI-AKI in DM, therefore, the investigation of antioxidants alternatives that promote renoprotection is of great importance.

The development of CI-AKI in DM was evidenced in this study with dysfunctions in renal function, renal hemodynamics and the installation of oxidative damage. Clinically CI-AKI is defined an increase in serum creatinine $\geq 0.5$ mg/dL or 25% increase of serum creatinine from the baseline value at 48 h after of contrast media administration [27].

The COQ-10 has demonstrated high therapeutic potential due to its antioxidant and anti-inflammatory activities in many injury models, including studies of nephrotoxicity by cisplatin and cyclosporine [15, 28, 29, 30]. Our results highlighted the role of COQ-10 in the modulation of pathophysiological processes induced by nephrotoxicity of IC, showing that the treatment with COQ-10 exerted a protective effect on the renal function of diabetic animals submitted to CI-AKI. The renoprotective effect was evidenced by the increase in inulin clearance and decrease in serum creatinine in DM animals that received IC and treatment with COQ-10.

Increased RVR and the decrease in RBF in DM after IC, as observed in this study, can be attributed to vasoconstriction due viscosity and osmolarity of contrast media. The vasoconstriction contributes to hypoxia and development of oxidative injury that culminate in endothelial dysfunction [4, 25]. Additionally, DM is associated with development of hypoxia inducible factors (HIF) that enhanced activity of renin-angiotensin system may also intensify the vasoconstriction via endothelin synthesis and increased effect of adenosine [2, 3]. In this study, treatment with COQ-10 demonstrated improvement in renal hemodynamics with reduced RVR and elevated RBF. Studies suggest that COQ-10 stimulates the production of prostaglandin-1 and prostacyclin, which aid in vasodilation, and reduce peripheral resistance by preserving the vasodilator nitric oxide, promoting the reduction of nitrogen dioxide to nitric oxide, helping to maintain this bioregulatory agent [11, 12].

In the present study, it was observed a significant increase of oxidative stress via TBARS, FOX and nitrate elevation and a reduction of thiols levels. Hyperglycemia increases oxidative stress in CI-AKI by activating stress-activated proteins kinase, functional proteins glycosylation, glucose autoxidation and the formation of reactive nitrogen species, such peroxynitrite, that has been related in the enhanced inflammation in diabetes by decreased nitric oxide bioavailability [10, 17, 31]. ROS production in DM has been linked to vasoconstriction, vascular cell hypertrophy and migration, endothelial dysfunction, modification of extracellular matrix proteins, and increased renal sodium reabsorption [3, 31]. Enhanced macrophage migration induces the release of inflammatory and profibrotic cytokines, stimulating greater ROS production. Thus, the oxidative stress induced by cytokine production in DM associated of contrast injury increase ROS establishing a vicious cycle [2, 32, 33, 34].
Despite its primary role in the production of ATP, COQ-10 is considered a substance of great antioxidant and anti-inflammatory activity, due capable of stabilize two free radicals to each molecule of COQ-10 in its redox cycle, is quickly recovered, may inhibit NF-κB and protein kinases, reduce free radical delivering them to recovery of antioxidants cycle, such vitamin E, efficiency in interrupting radical chain reactions such as lipid peroxidation, also to avoid nitrosative stress reacting [35, 36].

In this study, the treatment of diabetic animals with COQ-10 demonstrated the ability to preserve the reserve of systemic thiol anti-oxidant after IC administration. Intracellular antioxidants mechanisms such glutathione, a non-protein thiol, exercise role in neutralization of ROS, protecting against oxidative damage while their decrease contributes to the oxidative attack on cells. COQ-10 demonstrated to preserve glutathione in an animal model of cisplatin-induced nephrotoxicity by increase of selenium, necessary for the composition of glutathione [29, 37, 38].

In the present study, diabetic animals demonstrated mild tubulointerstitial changes typical of the development of diabetic nephropathy [39]. The histological changes observed in animals that received IC were due to the association of the insult caused by hyperglycemia and IC, reinforcing that the mechanism involved in the reduction of renal function is mainly related to renal hemodynamic changes and oxidative damage that favor the installation of IC-AKI. Our findings indicate that the administration of COQ-10 prevented the progression of the extension area with tissue damage after the use of IC. Considering that DM is a modifiable risk factor for IC nephrotoxicity, the implementation of preventive strategies with innovative pharmacological interventions, such as COQ-10, can establish a promising scenario and efficiently reverse the adverse effects of pathophysiology of the NIC.

**Conclusion**

This study is the first that demonstrated a renoprotection of COQ-10 in experimental model of risk factor of DM for CI-AKI. COQ-10 presented an antioxidant effect on the CI-AKI in diabetic rats, by improving function and renal hemodynamics, preserving morphology and reducing oxidative stress.

**Abbreviations**

Diabetes Mellitus: DM; contrast-induced acute kidney injury: IC-AKI; reactive oxygen species: ROS; Coenzyme Q10: COQ-10; Committee of Experimental Animals, University of Sao Paulo: CEEA; streptozotocin: STZ; iodinated contrast: IC; intraperitoneally: i.p.; intravenous: i.v.; Diabetes Mellitus+iodinated contrast: DM+IC; Diabetes Mellitus+iodinated contrast+CoenzymeQ-10:DM+IC+COQ-10; creatinine (Cr); renal blood flow: RBF; renal vascular resistance RVR; urinary thiobarbituric acid reactive substances: TBARS; trichloroacetic acid: TCA; standard error: SEM.

**Declarations**
• Ethics approval: The study was approved by the Ethical Committee of Experimental Animals, University of Sao Paulo (CEEA – protocol nº 055/15).

• Consent for publication: Not applicable

• Availability of data and materials: The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

• Competing interests: The authors declare that they have no competing interests.

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• Authors contributions: SMFC, CDF, MW and MFFV conceived this research and designed experiments, participated in the performed experiments and analysis, interpretation of the data, wrote the paper and revised of it. All authors read and approved the final manuscript.

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References

1. Pistolesi V, Regolisti G, Morabito S, Gandolfini I, Corrado S, Piotti G, Fiaccadori E. Contrast medium induced acute kidney injury: a narrative review. J Nephrol. 2018;31: 797–812.

2. Katsiki N, Fonseca V, Mikhailidis DP. Contrast-induced acute kidney injury in diabetes mellitus: Clinical relevance and predisposing factors. Could statins be of benefit? J Diabetes Complications. 2018;32(11):982-984.

3. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? Biomed Res Int. 2013;2013:123589.

4. Zhang X, Shi Z, Liu Q, Quan H, Cheng X. Effects of coenzyme Q10 intervention on diabetic kidney disease: A systematic review and meta-analysis. Medicine (Baltimore). 2019;98(24):e15850. doi:10.1097/MD.0000000000015850.

5. Lin K-Y, Shang X-L, Guo Y-S, et al. Association of Preprocedural Hyperglycemia With Contrast-Induced Acute Kidney Injury and Poor Outcomes After Emergency Percutaneous Coronary Intervention. Angiology. 2018;69(9):770-778. doi:10.1177/0003319718758140

6. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, Kosiborod M, Amin AP, Messenger JC, Rumsfeld JS, Spertus JA. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. JACC Cardiovasc Interv. 2014;7(1):1-9.

7. Ohshiro Y, Ma RC, Yasuda Y, Hiraoka-Yamamoto J, Clermont AC, Isshiki K, Yagi K, Arikawa E, Kern TS, King GL. Reduction of diabetes-induced oxidative stress, fibrotic cytokine expression, and renal dysfunction in protein kinase Cbeta-null Diabetes. 2006; 55(11):3112-20.

8. Wong PC, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. Int J Cardiol. 2012; 158(2):186-92.
9. Pisoschi AM, Pop A. The role of antioxidants in the chemistry of oxidative stress: A review. Eur J Med Chem. 2015;97:55-74.
10. Elmarakby AA, Sullivan JC. Relationship between oxidative stress and inflammatory cytokines in diabetic nephropathy. Cardiovasc Ther. 2012;30(1):49-59.
11. Yang YK, Wang LP, Chen L, Yao XP, Yang KQ, Gao LG, Zhou XL. Coenzyme Q10 treatment of cardiovascular disorders of ageing including heart failure, hypertension and endothelial dysfunction. Clin Chim Acta. 2015; 450:83-9.
12. Bentinger M, Brismar K, Dallner G. The antioxidant role of coenzyme Q. Mitochondrion. 2007; 7 Suppl:S41-50.
13. Abdollahzad H, Aghdashi MA, Asghari Jafarabadi M, Alipour B. Effects of Coenzyme Q10 Supplementation on Inflammatory Cytokines (TNF-α, IL-6) and Oxidative Stress in Rheumatoid Arthritis Patients: A Randomized Controlled Trial. Arch Med Res. 2015; 46(7):527-33.
14. Modi K, Santani DD, Goyal RK, Bhatt PA. Effect of coenzyme Q10 on catalase activity and other antioxidant parameters in streptozotocin-induced diabetic rats. Biol Trace Elem Res. 2006; 109(1):25-34.
15. Fouad AA, Al-Sultan AI, Refaie SM, Yacoubi MT. Coenzyme Q10 treatment ameliorates acute cisplatin nephrotoxicity in mice. Toxicology. 2010; 274(1-3):49-56.
16. Morsy MA, Ibrahim SA, Amin EF, Kamel MY, Abdelwahab SA, Hassan MK. Carvedilol ameliorates early diabetic nephropathy in streptozotocin-induced diabetic rats. Biomed Res Int. 2014; 2014:105214.
17. Fernandes SM, Martins DM, da Fonseca CD, Watanabe M, Vattimo Mde F. Impact of Iodinated Contrast on Renal Function and Hemodynamics in Rats with Chronic Hyperglycemia and Chronic Kidney Disease. Biomed Res Int. 2016;2016:3019410. doi:10.1155/2016/3019410
18. Fatima S, Al-Mohaimeed N, Arjumand S, Banu N, Al-Jameil N, Al-Shaikh Y. Effect of pre- and post-combined multidoses of epigallocatechin gallate and coenzyme Q10 on cisplatin-induced oxidative stress in rat kidney. J Biochem Mol Toxicol. 2015; 29(2):91-7.
19. Luchi WM, Shimizu MH, Canale D, Gois PH, de Bragança AC, Volpini RA, Girardi AC, Seguro AC. Vitamin D deficiency is a potential risk factor for contrast-induced nephropathy. Am J Physiol Regul Integr Comp Physiol. 2015; 309(3):R215-22.
20. Whiter P, Samson FE. Determination of inulin in plasm and urine by use of antrone. Journal of Laboratory and Clinical Medicine. 1954; 43(3):45–48.
21. Owen JA, Iggo B, Scandrett FJ, Stewar CP t. The determination of creatinine in plasma or serum, and in urine; a critical examination. Biochem J. 1954; 58(3): 426–37.
22. Gay C, Collins J, Gebicki JM. Hydrogen peroxide assay with the ferric - xylenol orange complex. Anal Biochem. 1999; 273(2):149-55.
23. Green LC, Wagner DA, Glogowski J, Skipper PL, Wishnok JS, Tannenbaum SR. Analysis of nitrate, nitrite, and [15N]nitrate in biological fluids. Anal Biochem. 1982;126(1):131-8.
24. Walker PD, Shah SV. Reactive oxygen metabolites in endotoxin-induced acute renal failure in rats. Kidney Int. 1990; 38(6): 1125-32.

25. Filomeni G, Rotilio G, Ciriolo MR. Cell signally and the glutathione redox system. Biochem Pharmacol. 2002; 64(5-6): 1057-64. G. L.

26. ELLMAN GL. Tissue sulfhydryl groups. Arch Biochem Biophys. 1959; 82(1): 70-7.

27. Ozkok S, Ozkok A. Contrast-induced acute kidney injury: A review of practical points. World J Nephrol. 2017; 6(3): 86-99.

28. Sato T, Ishikawa A, Homma Y. Effect of reduced form of coenzyme Q10 on cyclosporine nephrotoxicity. Exp Clin Transplant. 2013; 11(1): 17-20.

29. Maheshwari R, Balaraman R, Sen AK, Shukla D, Seth A. Effect of concomitant administration of coenzyme Q10 with sitagliptin on experimentally induced diabetic nephropathy in rats. Ren Fail. 2017; 39(1): 130-139. doi: 10.1080/0886022X.2016.1254659

30. Lu CJ, Guo YZ, Zhang Y, Yang L, Chang Y, Zhang JW, Jing L, Zhang JZ. Coenzyme Q10 ameliorates cerebral ischemia reperfusion injury in hyperglycemic rats. Pathol Res Pract. 2017 Sep; 213(9): 1191-1199. doi: 10.1016/j.prp.2017.06.005. Epub 2017 Jun 15. PMID: 28698101.

31. Ridzuan N, John CM, Sandrasaigaran P, Maqbool M, Liew LC, Lim J, Ramasamy R. Preliminary study on overproduction of reactive oxygen species by neutrophils in diabetes mellitus. World J Diabetes. 2016; 7(13): 271-8.

32. Hohmeier HE, Tran VV, Chen G, Gas R, Newgard CB. Inflammatory mechanisms in diabetes: lessons from the beta-cell. Int J Obes Relat Metab Disord. 2003; 27 Suppl 3: S12-6.

33. Zheng L, Kern TS. Role of nitric oxide, superoxide, peroxynitrite and PARP in diabetic retinopathy. Front Biosci (Landmark Ed). 2009; 14: 3974-87.

34. Satoh M, Fujimoto S, Haruna Y, Arakawa S, Horike H, Komai N, Sasaki T, Tsujioka K, Makino H, Kashihara N. NAD(P)H oxidase and uncoupled nitric oxide synthase are major sources of glomerular superoxide in rats with experimental diabetic nephropathy. Am J Physiol Renal Physiol. 2005 Jun; 288(6): F1144-52.

35. Nohl H, Kozlov AV, Staniek K, Gille L. The multiple functions of coenzyme Q. Bioorg Chem. 2001; 29(1): 1-13.

36. Zahedi H, Eghtesadi S, Seifirad S, Rezaee N, Shidfar F, Heydari I, et al. Effects of CoQ10 supplementation on lipid profiles and glycemic control in patients with type 2 diabetes: A randomized, double blind, placebo-controlled trial. J Diabetes Metab Disord 2014; 13: 81.

37. Sawicka E, Długosz A, Rembacz KP, Guzik A. The effects of coenzyme Q10 and baicalin in cisplatin-induced lipid peroxidation and nitrosative stress. Acta Pol Pharm. 2013; 70(6): 977-85.

38. Prangthip P, Kettawan A, Okuno M, Okamoto T. An improve of oxidative stress in rats by ubiquinone-10 and ubiquino- bioavailability after short- and long term coenzyme Q10 supplementation. 2016; 13(6): 647-659.
39. Sun H, Ge N, Shao M, Cheng X, Li Y, Li S, Shen J. Lumbrokinase attenuates diabetic nephropathy through regulating extracellular matrix degradation in Streptozotocin-induced diabetic rats. Diabetes Res Clin Pract. 2013; 100(1):85-95