Role of CoQ₁₀ on Some Biochemical and Histological Aspects of Kidney in Rats Exposed to Sodium Fluoride

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Abstract

This experiment was aimed to investigate the role of CoQ₁₀ to alleviating the functional alterations of kidney induced by sodium fluoride (NaF) in male rats. Twenty adult male Wister albino rats were randomly assigned into four equal groups and treated for 42 days daily as follows: first group was received drinking tap water and intubated with DMSO 1% and serving as control (group C); second group (group G₁) received sodium fluoride 100ppm in drinking tap water; third group (group G₂) received sodium fluoride 100ppm in drinking tap water plus intubated 10 mg /Kg B.W of CoQ₁₀ orally, whereas fourth group (group G₃) intubated 10 mg /Kg B.W of CoQ₁₀ only. Fasting blood samples were collected at 0, 21, and 42 days of experimental periods. Then sera was isolated for estimated serum creatinine, blood urea nitrogen (BUN) and peroxynitrite radicals concentrations, as well as catalase activities has been measured. At the end of the experiment the animals were sacrificed and sections from the kidney were taken for histopathological examination. The results revealed that rats received NaF (group G₁) for 42 days caused significant decrease in body weight and serum catalase activity, while a significant increase in the concentrations of serum creatinine, blood urea nitrogen (BUN) and peroxynitrite radicals accompanied with histopathological alterations of kidney were showed as compared to other experimental groups. On the other hand, administration of CoQ₁₀ to groups G₂ showed an improvement of physiological and histological alterations and keeping the kidney functions around the normal levels, manifested its protective effects against deleterious effects of NaF. It could be concluded that these results confirmed the antioxidant properties of CoQ₁₀ against nephrotoxicity induced by NaF in adult rats.

Key Words: kidney function, sodium fluoride, CoQ₁₀, antioxidant enzymes.
Introduction

Coenzyme Q10 is a unique lipid soluble vitamin-like substance synthesized endogenously (1) found with highest concentrations in heart, liver, kidney, pancreas and brain, with the lowest concentration in the lungs (2 and 3). It has been found that CoQ10 play unique role in mitochondrial bioenergetics (4) and in the electron transport chain (ETC) as an electron carrier from enzyme complex I and enzyme complex II to complex III (5). Thereby, it is participates in aerobic cellular respiration and generated energy in the form of ATP for cellular functions and metabolism (1 and 5), since no other molecule can perform this function. Wherefore, CoQ10 considered as the third most sold dietary supplement in the United States after omega-3 fatty acids and multivitamins (6). Mutations in the genes involved in the biosynthesis of CoQ10 causing disruption of mitochondrial bioenergetics and induced oxidative stress (4 and 7) which related to various types of mitochondrial diseases.

Many researchers suggested that dietary supplement of CoQ10 countering some of tissue damage induced by free radicals such as nephrotoxicity , inflammation and apoptosis (8and9), liver and heart injury (10and11) via its cytoprotective , antioxidant and anti-inflammatory properties (12,13and 14). Also, exogenous supplementation of CoQ10 ameliorating the bioenergetics impairment in some mitochondrial myopathies and in cardiomyopathy, may be due to an increase respiratory rate (15 and 16). On the other hand, administration of CoQ10 (Ubiquinol) caused an improvement of renal injury and a decrease in renin-aldosterone axis in patients with lithiasis(17) and effectively ameliorates renal function probably due to its antioxidant effect (8). Thus, ubiquinol may be a candidate for the treatment of patients with kidney disease (18).

Fluoride anions are present in ground water and drinking water and can be transported by wind due to dust, fertilizers and volcanic activity (19). Fluorine is used in aluminum production (20), in pesticides, fungicides, insecticides adhesives and glues (21). Furthermore, its compounds are mostly used to keep from oral caries (21) and to reduces the decay of teeth enamel (23). Fluoride administration substantially enhanced fluoride accumulation, caused metabolic disturbance activities and lipid peroxidation(LPO) via inhibit...
certain antioxidant enzymes and reduce total serum protein (24,25 and 26). The toxic level of fluoride have been associated with nephrotoxicity in animals and humans (27 and 28) that may be due to release of fluoride from fluorine-containing substances. At the higher concentration of fluoride, the kidney function was impaired and exhibited to depressed clearance of crystalloids, enhanced elimination of amino acids and cause inhibition of enzymes that required for action of antidiuretic hormone (29). Considering all of these facts, the aim of the present work was designed to investigate the effect of CoQ10 in ameliorating the kidney dysfunctions in sodium fluoride treated rats.

Materials and Methods
In this experiment twenty adult male Wister albino rats, weighed (190g.- 250g.) were used. Animals in all periods of the experiment were housed in plastic cages in the animal house of the College of Veterinary Medicine – University of Baghdad and had free access to pellets diet and water ad libitum water along the experimental period. Rats were divided randomly into four equal groups and were handled daily as follows for 6 weeks: group- C: rats in this group rats were received ordinary tap water plus intubated dimethylsulfoxid (DMSO) 1% and served as control; group-G1: in this group rats were administered 100ppm of sodium fluoride in tap water; while rats in group-G2 were intubated daily 10 mg/kg BW of CoQ10 plus received ordinary tap water containing 100 ppm of NaF and group-G3 were intubated CoQ10 only at the same dose of group-G2.

Fasting blood (for 10-12 hr.) samples were collected at zero, 21 and 42 days of the experimental periods. Blood was drawn by retro-orbital sinus technique according (30) from anesthetized rats by intramuscular injection of (Ketamine 90 mg/kg B.W. and Xylazine 40mg/kg B.W.) using Micro-Hematocrit capillary tubes. Blood samples were kept in gel tube, then centrifugation for 15 minutes at 3000 rpm. Serum samples were isolated and frozen at -18°C until analysis. By using kits (products of Bio System, Agappy Switzerland) for estimated the concentrations of serum creatinine according to (31), blood urea nitrogen (BUN) as described by (32). Furthermore, serum peroxynitrate radical concentration was measured according to (33) and serum catalase activity was determined according to the method of (34). At the end of experiment rats were anesthetized and sacrificed and immediately kidney were excised, blotted, and preserved in 10% formalin solution, then embedded in paraffin, slices and staining with hematoxylin-eosin method for histological examination (35). Statistical analysis of data was done using SPSS software version 9.1. using Two-Way Analysis of Variance (ANOVA) followed by post hoc least significant difference (LSD) test. Results were expressed as mean ± SE. For all analysis, the level of statistical a significance was set at P<0.05 (36).

Results:
The results of the present work showed a significant (p<0.05) elevation in serum creatinine concentration at 21 and 42 days of the treatment in G1 and G2 groups compared to control and G3 groups (figure 1-A). At the end of the experiment a correction of kidney dysfunction (i.e. decrease in serum creatinine) was observed in group G2 that received NaF plus CoQ10 (0.61±0.01) comparing to the mean value in G1 group (0.85 ±0.01).

In the present study, a significant (P<0.05) elevation in serum BUN concentration at 21 and 42 days of the
experiment in group G1 and group G2 was observed in comparison with control and G3 groups (figure 1-B). Further, no significant (P > 0.05) differences were recorded between control and G3 groups at two treated periods (21 and 42 days) of the experiment. In comparison between periods, G1 and G3 treated groups recorded significant (P < 0.05) increase in serum BUN at 21 and 42 days compared to zero point.

Rats received NaF in drinking water group G1 and that received NaF plus intubation of 10 mg/kg B.W. of CoQ10 (group G2) showed significant (P<0.05) increase in serum peroxynitrite concentration started at 21 days of treatment in comparison with control and G3 groups (figure 1-C) and continued in its elevation until the end of the experiment at 42 days. Otherwise, a significant (P<0.05) decrease in this parameter was observed at 42 days in group G3 with the mean value (32.39±1.0) comparing to control (36.09±1.29). In comparison between periods, control and G2 groups showed no significant (P>0.05) differences between the experimental periods, whereas sodium fluoride treated group (G1) recorded significant (P<0.05) increase at day 42 comparing to zero and 21 days.

On the other hand, the results showed significant (P<0.05) decrease in serum CAT activity after 21 days in G1 and G1 treated groups and continued in its decrement until the end of experiment in the same groups (figure 1-D).
Figure (1) Effect of sodium fluoride and CoQ10 on serum concentrations of (A) creatinine, (B) blood urea nitrogen (BUN), (C) peroxynitrite and (D) catalase in adult male rats.

Values are represented as mean ±SE. Different small letters denotes the presence of significant differences (p < 0.05) between groups. Different capital letters denotes the presence of significant differences (p < 0.05) within group. Control: rats received tap water; G1: rats received tap water contain NaF 100 ppm; G2: rats received tap water contain NaF 100 ppm Plus orally garaged CoQ10 (10 mg/kg B.W.); and G3: rats orally garaged CoQ10 (10 mg/kg B.W.).

Histopathological examination of kidney sections of control rats showed normal structure of the kidney with devoid of pathological lesions figure (2). In sodium fluoride treated rats (group G1) kidney sections showed renal damage characterized by hydropic generation with interstitial inflammatory infiltration of mononuclear cells (MNCs) figure (3) and dilation of Bowman's space may be due oxidative stress with presence of hyaline casts in renal tubules compared to figure-2. Whereas, rats exposed to sodium fluoride plus CoQ10 (group G2) caused an ameliorating the kidney damage characterized by decrease of hydropic generation and inflammatory cell infiltration with mild congestion and slight edema figure (4). No pathological changes with normal architecture of kidney tissue sections has been showed in rats kidney intubated CoQ10 only (figure 5) as compared to control.
Figure 2: Cross section of rat kidney of control showed normal cellular and tubular structure kidney. 40X (H & E stain).

Figure 3: Cross section of rat kidney treated with NaF (group G1) for 42 days, revealed renal damage characterized with interstitial inflammatory infiltration of mononuclear cells (MNCs) (1) and dilation of Bowman's space (2) and distal tube (3) 40X (H & E stain).

Figure 4: Cross section of rat kidney treated with NaF and CoQ10 (group G2) for 42 day represents mild dilation of Bowman space (1) with slight edema (2) 40X (H & E stain).

Figure 5: Cross section of rat kidney treated with CoQ10 (group G3) for 42 day. Shows normal histological structure of the kidney without of pathological lesions 40X (H & E stain).
Discussion

The kidney is a target organ for potential fluoride toxicity. Data in the present study showed that NaF caused significant increase in serum creatinine and BUN (group G1). These results were agreement with (37). It has been shown that fluoride ions caused directly inhibit glycolysis, by inhibiting the enzyme enolase in renal cells, which is often compensated by using alternative energy-producing pathways that leading to renal cellular dysfunctions (38) correlated with increased calcium and phosphate urinary excretion (39), as well as, an increased degradation of collagen and/or inhibition of collagen synthesis by NaF (40) leading to alterations in glomerular filtration rate (GFR) (41). The results manifested a significant reduction in serum creatinine and BUN concentrations in group G2 compared to group G1, indicating that CoQ10 could be reversed the toxic effect of NaF on renal tubular cells and improvement kidney functions due its antioxidants properties.

Concerning the oxidant/antioxidant status, the result showed a significant decrease in serum catalase activities with significant increase in peroxynitrite concentration in group G1 compared to control suggesting a case of oxidative stress induced after exposure to NaF. This result is in accordance with other studies (25,42 and 43). Further, it has been reported that fluoride intoxication resulted to induce oxidative stress (OS) with an excessive generation of reactive oxygen species (ROS) such as superoxide anion (O$_2^-$), hydrogen peroxide (H$_2$O$_2$) and hydroxyl radicals (OH) (44), which have been implicated in the initiation and/or progression of nephrotoxicity (45). Such changes in these biomarkers related with oxidant–antioxidant status and histological structures of kidneys in group G1 that may be caused LPO, DNA and proteins damage leading to renal dysfunction (41 and 46). So, it impair the catalase activity in catalyzes of hydrogen peroxide to water and oxygen and prevent the protecting of cell membrane against LPO induced by ROS (42). Peroxynitrite is a key element in refraining the contrasting parts of NO in pathology and physiology. It is an oxidant and nitrating agent, so when generate in excess in a long period will result in damage a wide range of cell constituent (47). Oxidation of cofactors of antioxidant enzyme either by direct or free-radical-dependent mechanisms causing depletion of these enzymes (48) leading to disruption of cell signaling pathways and induction of both cell necrosis and apoptosis (47). Otherwise, elevation in environmental oxidants including NaF caused elevation in of ROS give rise to mitochondrial dysfunction such as, loss of mitochondrial transmembrane potential, release of cytochrome C and calcium ions from mitochondria, leading to activation of caspase-3 and nuclear condensation with elevation of peroxynitrite (49and 50).

A significant increase in the activity of serum CAT enzyme (group G2) compared to G1, indicating a role of CoQ10 in attenuating oxidative stress-induced by NaF. Such results came in accordance with (17, 51 and 52). CoQ10 is an important micronutrient acting on the electron transport chain of the mitochondria through supporting the synthesis of adenosine triphosphate (ATP) and acting as a potent antioxidant (53 and 54). The protective role of CoQ10 was indicting by preventing a significant loss of mitochondrial mass via ; increasing mitochondrial number and volume density, suggesting an induction of mitochondrial biogenesis (55), or by maintaining the mitochondrial membrane potential, supporting synthesis of ATP and inhibiting ROS generation, thereby, may
be protecting the cells against oxidative stress (53,56 and 57). So, it could be suggested that oxidative stress in group (G1) can be ameliorating/suppressed with CoQ10 treatment attributed to its antioxidant properties.

References


43. Nabavi, S. M. (2013). In vivo protective effects of gallic acid isolated from peltophyllumpertalut against sodium fluoride-induced oxidative stress in rat erythrocyte.


to pathogenesis and neuroprotection. Eur J Pharmacol 58.