



CoQ10 Improved Liver Function and Redox Status in Pollution-exposed Workers

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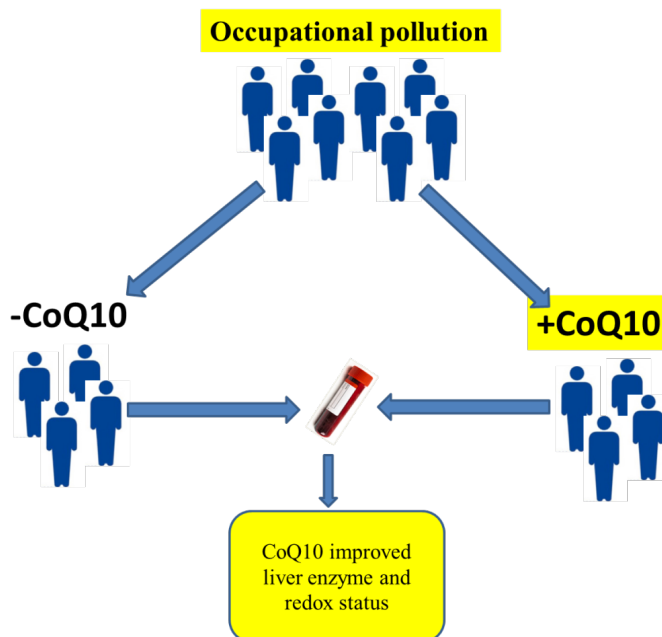
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ABSTRACT

Chronic exposure to workplace pollution has been increasingly reported as a potential hazard for the induction of diseases or involved in the pathogenesis of already present conditions. The aim of the present randomized, double-blind, controlled, clinical trial was to investigate the protective role of CoQ10 in improving liver function and redox status of occupationally exposed workers. To do so, blood samples were collected from 132 participants working in a polluted environment for a period of longer than 1 year, with most of them working for a period between 5-10 years. They were then divided into a control group (n=60) receiving placebo therapy and an intervention group receiving CoQ10 (200mg/day) therapy for 2 months. Blood samples were withdrawn and the serum was then analysed for total antioxidant capacity (TAOC), malondialdehyde (MDA), glutathione-peroxidase enzyme (GSH-Px), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, and bilirubin. Results: CoQ10 has significantly ($P < 0.05$) increased TAOC and GSH-Px alongside significantly ($P < 0.05$) reducing MDA. Liver function test has shown no changes regarding ALT, ALP, and albumin, with a significant reduction of bilirubin and AST. Moreover, weight-related indices (body weight, BMI, waist and hip circumferences) have shown non-significant changes after CoQ10 therapy. Systolic blood pressure significantly reduced in treated group compared to control group. Conclusion: CoQ10 could be advised as a supplement to protect against the hazard of exposure to pollution.

Graphical Abstract



Introduction

Pollution exposure has increasingly become an important risk factor for public concern resulting in increased morbidity or mortality due to its impact on exaggerating the condition of already sick people or inducing new diseases on its own; These hazards doubled in workers close to the source of pollution¹. These include, but are not limited to, workers in various jobs like metal processing, car repair, mining, coal burning and dealing with petroleum have increased risk of heavy metals exposure or even heavy metals linked adverse effects and intoxication². This pollution is then represented as a causative agent inducing pathophysiological changes in terms of proinflammatory remarks and redox imbalances^{3,4}.

One of the major health concerns nowadays is heavy metal-induced cellular toxicity. The usage of heavy metals in various industrial fields can produce environmental contamination and result in severe hazards to health. The primary cellular response to heavy metal toxicity is oxidative stress induction, which can be defined as an imbalance in the redox system. The

increase in oxidative stress and free radical generation are associated with the damage to macromolecular and activation of specific cell survival/ death pathways^{5,6}.

Heavy metal exposure can produce oxidative stress and this in turn, is linked to many pathological conditions such as increased risk of neoplasm, premature cardiovascular disease, infertility, diabetes, renal failure, neurological disorders or even developmental disorders. In recent years, enter-relation among heavy metal toxicity, oxidative stress initiation and activation of specific signaling pathways become important areas for research to show the role of heavy metal in many pathophysiological conditions. The role of heavy metals in oxidative stress induction and activation of many signaling pathways is not fully understood, however, important and well-related signaling pathways involved⁷

Co-enzyme Q10 (CoQ10) is a co-factor in enzyme complexes that participate in oxidative phosphorylation in the mitochondrial production of adenosine triphosphate. In addition, CoQ10 serves as an antioxidant or free radical scavenger. Ubiquinol, a reduced

form of CoQ10, is potent lipophilic antioxidant and can regenerate and recycle other antioxidants in the body. Numerous other functions of CoQ10 have been described, such as cell signaling, membrane stabilization and gene expression⁸.

In the present study, we aimed to determine the impact of supplementation of CoQ10 on improving liver function tests including liver enzymes (alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, and bilirubin). Moreover, the impact of CoQ10 was also assessed on redox parameters via measuring total antioxidant capacity (TAOC), malondialdehyde (MDA), and glutathione peroxidase (GSH-Px) in individuals at high risk at their workplaces for occupational pollution.

Materials and Methods

Study Settings and Design: This study is designed as a randomized, double-blind, placebo-controlled 2-month clinical trial. Participants work in an industrial career (car repairing, gas station, local generators, and painting) for at least 1 year. The study protocol is approved by the Ethics Committee for Medical Research of Mosul University as well as the Research Ethical Committee of Nineveh Health Directorate. Consent form signed by participants to participate in this study. Exclusion criteria include females and males who are under 18 and over 75 years old, participants who are alcoholics. If a person has less than the one-year duration of working in the industrial field has been excluded. Males who are intermittently exposed to industrial pollution were excluded. Patients with chronic diseases, such as diabetic patients, patients with renal failure gastrointestinal diseases, stroke, and neurological disorders were excluded.

Inclusion criteria: participants were males, aged between 18–75 years, working in different industrial fields that are exposed to industrial pollution of heavy metals. These subjects include workers in car-repairing, gas stations, local generators, and painting.

The number of participants as cases were 72, while the number of participants as control was 60, age groups were (18 -75 years), and they were randomly divided into two groups. The case group was giv-

en CoQ10 (NATROL® company /USA) at the dose of 200mg per day for two months. Blood pressure, body weight, hip circumference, or waist circumference were recorded initially and after therapy.

Blood was withdrawn from patients and serum was separated and frozen at -20°C for further analysis. The serum samples were analysed for total bilirubin, albumin, liver enzymes (ALT, AST, and ALP), TAOC, MDA, and GSH-Px. TAOC was measured by colorimetric method using the TAOC assay kit supplied by (Elabscience®, USA). GSH-Px was measured by colorimetric method using the GSH-Px assay kit supplied by (Elabscience®, USA). MDA, were measured by the ELISA method using the MDA ELISA kit supplied by (Elabscience®, USA). ALP was measured by colorimetric method using the alkaline phosphatase assay kit supplied by (Giese Diagnostic®, Italy). ALT was measured by colorimetric method using the ALT Assay kit supplied by Linear chemicals (Spain). AST was measured by colorimetric method using the AST assay kit supplied by Biolab (France). Albumin was measured by colorimetric method using an albumin assay kit supplied by Biolab (France). Bilirubin was measured by colorimetric method using the bilirubin assay kit supplied by Biolab (France).

Results

The duration of occupation exposure of the participants in the study is tabulated in Table 1. The participants were most often exposed to causative agents for a period between 5-10 years.

The results express no significant change in body weight, BMI, hip circumference, or waist circumference after two months of therapy. Systolic, but not diastolic, blood pressure in participants group exposed to pollution were significantly ($p < 0.05$) reduced when they were given CoQ10. The age of all participants ranged between (18-75) years with the average for the control group (35 ± 5) and CoQ10 treated group (42 ± 8) years (Table 2).

The change in TAOC in the CoQ10 receiving group indicate a significant increase in TAOC level with a p-value of 0.001; while for the placebo group, the p-value was 0.177. Glutathione peroxidase also dis-

played a significant change in the CoQ10 treated group compared to the placebo group with a p-value of 0.001 and 0.446, respectively. MDA increase in oxidative stress condition. In the current study, we can detect a decrease of MDA value in the group that received CoQ10 while changes in the control group were insignificant; the calculated p value was 0.001 for the CoQ10 group versus 0.438 for the placebo group (Figure 1).

The ALT activity measurement indicates that there is a significant reduction in its activity in the CoQ10 receiving group after two months of management with a p-value of 0.005, while in placebo receiving group reduction is insignificant with the p-value equal to 0.316. The reduction in the activity of AST is noted in both the placebo and CoQ10 groups, but the p-values indicate that the change is significant in the CoQ10 group while it occurs by chance in the placebo group. The activity of ALP is reduced to a minor extent in both groups and p values indicate that there is no significant effect of CoQ10 on the activity of alkaline phosphatase after two months. The result shows no significant change in the concentration of serum albumin after two months of CoQ10 administration. The last measured parameter of liver function tests is total bilirubin concentration. The result showed a reduction in total bilirubin concentration from 0.486 to 0.372 mg/dl with p p-value equal to 0.003 (Figure 2).

Discussion

The present study conducted on pollutant exposed workers and the outcomes revealed that CoQ10 has positively modulated the blood pressure, redox parameters, and liver enzymes in participants who have been working in area of exposure to heavy metals for long term. The weight indices were not changed after two months of CoQ10 use.

The weight assessment of the patients was based on four basic parameters which include weight, hip circumference, waist circumference, and BMI. The outcome has ultimately shown no significant change of body weight indices in the group that received CoQ10 versus placebo group. Many studies were conducted to assess the effect of CoQ10 and weight and their out-

comes were in line with the findings of this study^{9,10}. A Muhtaroglu study succeeded in finding a negative correlation between CoQ10 level and BMI. Besides, it is mentioned that endogenous CoQ10 synthesis might not compensate great demand for lipophilic antioxidants in obese individuals explaining the negative role of CoQ10 on body weight indices¹¹. Conversely, body weight indices improved by CoQ10¹²⁻¹⁴, and this change has been linked to leptin level modulation, since administration of CoQ10 results in reduced leptin levels. Leptin can stimulate lipolysis and inhibit lipogenesis by affecting the activity of the enzymes in the pathways for the synthesis and breakdown of fatty acids, although an increased level of leptin may be associated with leptin resistance and increased weight^{12,13}. The effect of the administration of CoQ10 on BMI at longer duration and higher doses needs further studies.

The results of the current study regarding blood pressure agrees with many researches and meta-analysis data^{15,16}. There is a reduction in systolic, but not diastolic blood pressure, to a significant extent. This reduction in blood pressure values showed a slightly lower improvement compared to the conducted result of the meta-analysis study with a decrease of about 8 units for systolic and 5 units for diastolic blood pressure when the result of blood pressure lowering ranges for systolic blood from 10 to 21 mm Hg and for diastolic from 7 to 16 mm Hg in meta-analysis study. The participants in meta-analysis were hypertensive individuals, while in the current study, the participants range from normotensive to prehypertensive¹⁶. This could be explained in the context of oxidative stress invoke vasoconstriction and CoQ10 is a potent lipid-soluble antioxidant with the ability to offset this vasoconstriction and thus lower blood pressure¹⁶. Additionally, CoQ10 encourage vasodilation via a direct effect on the vascular smooth muscle and endothelium. The studies of hypertensive patients treated with co-enzyme Q10 showed decrease peripheral resistance with lowering of blood pressure and unaffected cardiac output. It should be noted that in normal animals or humans, co-enzyme Q10 has no vasodilating or hypotensive effect. This indicates that the hypotensive effect of co-enzyme Q10

Table 1. Period of exposure to causative agents at workplace.

| Time of exposure | Placebo | CoQ10 |
|---------------------|---------|---------|
| Occupation exposure | n (%) | n (%) |
| <5 Years | 24 (40) | 30 (42) |
| 5 to 10 years | 27(45) | 24(33) |
| >10 Years | 9(15) | 18(25) |

Table 2. The impact of CoQ10 on body weight-related indices and blood pressure.

| Parameters | -CoQ10 Baseline | -CoQ10 At the end | +CoQ10 Baseline | +CoQ10 At the end |
|--------------------------|-----------------|-------------------|-----------------|-------------------|
| Age (Years) | 35±5 | | 42±8 | |
| BMI (kg/m ²) | 27.38±4.69 | 27.52±4.75 | 29.11±4.68 | 28.81±4.51 |
| Weight(kg) | 82.25±18.4 | 82.47±18.7 | 84.9±14.1 | 83.7±13.5 |
| Waist circumference (cm) | 92.25±16.4 | 92.5±16.4 | 96.9±11 | 95±9.95 |
| Hip circumference (cm) | 100.8±9.07 | 100.7±8.96 | 102.3±7.2 | 101.7±7.34 |
| SBP (mmHg) | 130±12 | 132±12 | 135±12 | 127±6* |
| DBP (mmHg) | 81±7 | 80±8 | 85±7 | 79±7 |

Data expressed as mean±SD, *significant differences as compared to other groups at p value p<0.05, BMI=body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure

is specific to the state of exaggerated oxidative stress condition that occurs in hypertensive patients. Co-enzyme Q10 has been shown to target the expression of many genes, particularly those involved in signaling and metabolism and this may have a role in blood pressure reduction¹⁶.

The TAOC reduces due to exposure to occupational pollution, which is mainly due to heavy metals exposure, thereby increases oxidative stress and results in the exhausting of TAOC within the body. The number of epidemiological studies regarding TAOC and air pollution remains limited. One study in India reported increased reactive oxygen species (ROS) generation after exposure to environmental pollution and this resulted in a depletion in TAOC¹⁷. Another study among elderly people who lived in Mexico City, showed low TAOC level because of high air pollution exposure¹⁸.

There are many studies suggest that there is an increase in the level of MDA is due to an increase generation of free radicals due to exposure to various pollutants this in turn results in lipid peroxidation and damage to cell membranes which act as easy targets for free radicals since it contains a large proportion of unsaturated fatty acid^{19,20-22}. The rise in MDA is an indication of the occurrence of oxidative stress among workers exposed to different industrial pollutants. This increase in the concentration of MDA is due to the increased generation of free radicals during exposure to different types of industrial pollutants (heavy elements) such as cadmium and lead and their accumulation in the body, which in turn leads to an increase in lipid peroxidation, which results in oxidative damage in the cell membrane. Cell membrane is the main target of free radicals since it contains mul-

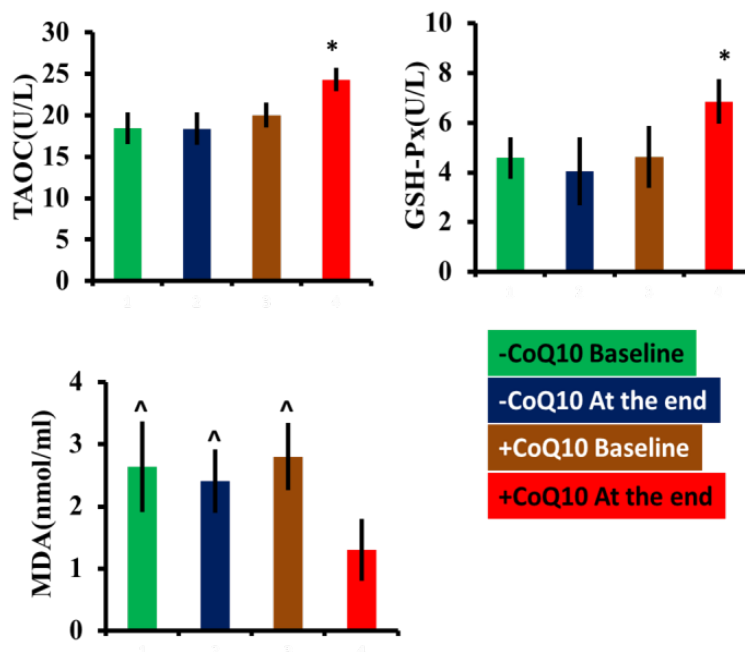


Figure 1. Redox parameters improved by CoQ10 therapy. Data expressed as mean±SD. * $P < 0.05$. * as compared to all other groups, ^ as compared to the CoQ10 treated group at the end of two months of therapy. TAOC=total antioxidant capacity, GSH-Px=glutathione-peroxidase, MDA=malondialdehyde, CoQ10=Coenzyme Q10 or Ubiquinone.

tiple polyunsaturated fatty acids and is rich in double bonds, and this leads to increased MDA concentration which is one of the main final products of lipid peroxidation^{20,23}. Heavy elements act as catalysts for ROS production and this leads to lipid peroxidation, in addition to the depleting of antioxidants^{24,25}. The extent of change in MDA concentrations varies and can be correlated with periods of exposure. This study is consistent with the findings of those who have mentioned that exposure to industrial pollutants leads to a significant increase in MDA concentration, and this is directly proportional to the increase in periods of annual exposure^{20,26}.

The activity of GSH-Px can also change in population exposure to occupational pollution. The association between GSH-Px activity and pollution exposure has been inconsistent across epidemiological studies. Some studies have found that lower GSH-Px activity in pollution conditions^{26,27}, while others have found that GSH-Px activity is higher in pollution conditions²⁸. It is suspected that individuals' long-term exposure to pollution might have decreased antioxidant enzyme

activity due to long-term oxidative stress. This suggestion was supported by previous experimental and human studies^{26,29,30}.

In the line of the present study, CoQ10 has been reported to exert antioxidant effects against ROS-environmental contaminants. For instance, CoQ10 has reduced oxidative stress in Inuit people due to their diet-rich with prooxidants³¹. Environmental contamination with chemicals (Bisphenol A- or Arsenic- or Lead Acetate-Induced Oxidative stress) have been tackled by CoQ10 and restored infertility³²⁻³⁴. Moreover, anticancer induced oxidative tissue damages have been dampened by CoQ10³⁵.

There are many studies indicating that the CoQ10 has a protective effect on the liver either by direct antioxidant effect or by its anti-inflammatory effect^{9,36}. The results of this study confirmed that CoQ10 has a beneficial effect on liver enzymes and it is associated with the reduction in both the activities of ALT and AST. The result in the placebo group showed no difference between the measurement of both ALT and AST. This may be in part because the

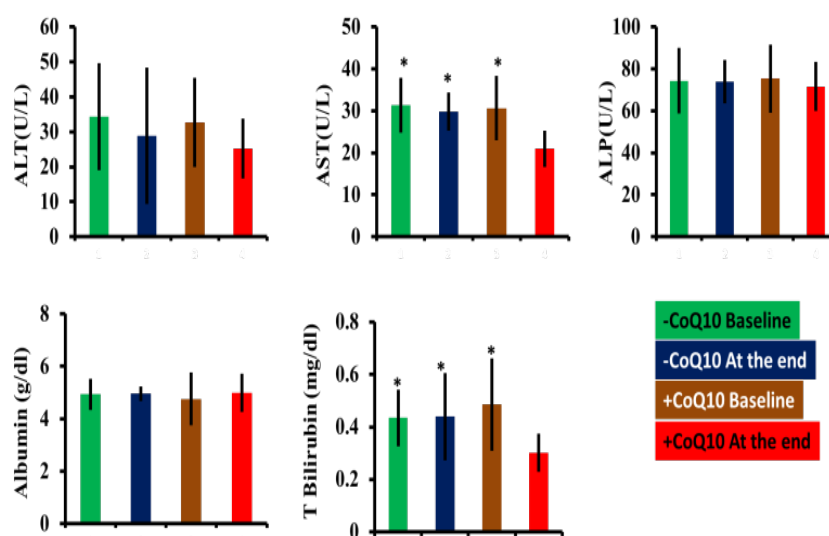


Figure 2. Liver function parameters improved by CoQ10 therapy. Data expressed as mean±SD. *P<0.05. * as compared to the CoQ10 treated group at the end of two months of therapy. ALT=alanine aminotrasferase, AST=aspartate aminotrasferase, ALP= alkaline phosphatase CoQ10=Coenzyme Q10 or Ubiquinone.

liver's transferase enzymes are elevated related to oxidative stress and in the CoQ10 receiving group there is a reduction in the generation of free radicals and subsequent oxidative stress occurrence⁹. As a result, damage to liver cells is minimized and the death of hepatocytes is reduced so the amount of released transferase will be reduced⁹. The results of the current study agree with the results of^{37,38}. Also, many animal studies show the same protective effect of CoQ10 on the liver, it showed that CoQ10 usage was associated with a decrease in both improvement in the level of ALT and AST^{39,40}.

Many studies are conducted to assess the effect of occupational pollution on liver enzymes which showed varying results between insignificant increase to significant increase that may be in part due to different experimental settings with different impacts and different exposure periods⁴¹. Alkaline phosphatase activity changes with pollution also range from significant reduction in their activity to insignificant changes. The reduction of their activity may result in part due to the replacement of magnesium co-factor in this enzyme by lead⁴². The effect of CoQ10 on the level of alkaline phosphatase showed no significant results and the results in both CoQ10 treated group and placebo group are parallel. This indi-

cates that the administration of CoQ10 has shown no improvement in ALP activity. The results agree with the studies reported no significant change in ALP activity^{43,44}. Decreased activity of ALP may result in part from the replacement of lead for magnesium and zinc⁴². Others expect that the cause of reduced alkaline phosphatase activity in pollution conditions results in part from the low level of zinc or magnesium⁴⁵. In a related issue, the result of animal studies showed an increase in the activity of alkaline phosphatase by administration of CoQ10 and that has a beneficial effect in many species. Supplementation with CoQ10 may increase mitochondrial Mg²⁺ and enhance alkaline phosphatase activity in some species^{42,46}.

Exposure to occupational pollution may result in a decreased ability of the liver to synthesize albumin and this may have appeared as a reduction in its level or might be due to pollution induced oxidative stress leading to kidney damage which may result in leaks of albumin out of the body via excretion¹⁹. The results of the current study showed no significant change in serum albumin concentration in either CoQ10 or placebo-receiving groups. The results of some studies indicate a significant change in the serum albumin perhaps due to higher doses used and longer periods this may be due to that the majority of these studies

are performed in animal models or persons with obvious liver or kidney impairment with previously altered albumin levels^{42,47}.

The level of total bilirubin shows a significant reduction in the CoQ10-treated group compared to the placebo group. This indicates that CoQ10 has a protective effect on the liver. In addition, it may improve red blood cell survival and one result of this is reduced total bilirubin. This effect may in part be due to the potent antioxidant and anti-inflammatory effect of CoQ10⁴⁸. There are various studies performed to illustrate the effect of the administration of CoQ10 with total bilirubin concentration and the result of this study agrees with the results of many studies^{40,49}. On the other hand, no significant change in total bilirubin is seen in another study⁴⁹ and that may be in part due to lower dose or duration of management, also since the concentration of total bilirubin is not affected to a significant extent in participants so no significant change is detected. Another liver function test parameter that shows change

due to occupational pollution is total bilirubin. Many studies indicate that exposure to occupational pollution may be associated with increased bilirubin levels both by direct damage to the liver which may result in reduced efficacy of the liver to extract bilirubin and also by increasing breakdown of red blood cells due to oxidative stress^{19,50}.

Conclusion

The environmental pollutant exposure at workplace potentially modulates redox balances and liver damage. CoQ10 dampens this potential deleterious impact via reducing lipid peroxidation and maintaining higher antioxidant levels alongside reduced liver enzyme and liver parameters against damage induced by environmental pollutant. A recommendation should be directed toward indicating these supplements in high-risk group individuals heavily exposed to workplace pollution. □

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