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ORIGINAL ARTICLE

Ubiquinone Supplementation Lessens the Negative Impacts of Occupational Lead Exposure by Reducing Inflammation

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Lead occupational exposure has been increasingly reported by healthcare providers as an important challenge in industrial settings. Ubiquinone is a natural substance that has a role in the electron transport chain and oxidation-reduction pathway. In this study, we evaluated the effects of ubiquinone on inflammatory markers in workers who were exposed to lead in their routine daily work, as determined by measurement of lead levels in their blood at the start of the study, and compared to the control group. This study is a randomized, blind, placebo (control (two-month clinical trial. 61 people who had spent at least a year in an industrial environment were divided into two groups. In the ubiquinone group, 31 participants received 200 mg/day of ubiquinone-containing capsules for two months, and in the placebo group, 30 participants received a placebo capsule of starch daily for two months, At the end of the study, there was a withdrawal of one participant from the ubiquinone group and two participants from the placebo group. The inflammatory biomarker high-sensitivity C-reactive protein was measured using a turbidimetric immunoassay, while TNF-? and IL-6 plasma levels were determined using an ELISA. These measurements were done at the start of the study and after two months to compare the results of these parameters in the ubiquinone and placebo groups. After two months of ubiquinone supplementation, there was a statistically significant improvement in TNF- and IL-6 concentrations, but it did not affect CRP levels in the study participants.

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The industrial revolution of the 18th century led to major changes in working conditions so exposure to heavy metals became an inevitable risk..[1] The current work environment has emerged as one of the most significant global public health concerns.[2] The interaction between the environment and the biological system is one of the major factors that govern an individual's health. The danger of exposure to heavy metals and their associated negative effects is increased by numerous activities, such as those that deal with petroleum, metal processing, vehicle maintenance, mining, and coal burning.[3] Nowadays, a series of studies have shown that heavy metals are the primary risk factors linked to the emergence of several pathophysiological illnesses. Essentially, the pathways by which they cause harmful consequences to involve inflammation and oxidative stress in the heart, lungs, and blood vessels.[4,5]

Many studies show that exposure to heavy metals that arise from occupation or environmental pollution results in low-grade inflammation. At the cellular level, the alteration of metabolic homeostasis is the main cause of heavy metal toxicity. This happens as a result of the accumulation of an excessive amount of heavy metal within different tissues. The metallic deposits then interfere with enzymatic, metabolic, and mitochondrial processes, which impair biological function.[6] The pharmacokinetics of each metal, as well as the route of exposure, determine how much of this malfunction and subsequent injury occurs.[7]

Lead is a naturally occurring heavy metal that is primarily found in conjunction with sulfur, and is distinguished by its high density, malleability, weak conductivity, and corrosion resistance. Because of its physio-chemical properties, lead is widely used in a variety of industries. The main ways that humans are exposed to lead are through the consumption and inhalation of contaminated foods, drinks, air, and soil.[8]

In the blood, lead has a half-life of about 30 days, after which it transfers into soft tissues like the kidneys, brain, and liver before being dispersed as lead phosphate to bones, teeth, and hair.[9]

Lead poisoning results in the production of ROS (Reactive Oxygen Species) like hydroperoxide, hydrogen peroxide, and singlet oxygen. These free radicals are produced by lead exposure. When ROS and antioxidant defences are out of balance, the body experiences oxidative stress. Oxidative stress causes the release of pro-inflammatory mediators, cellular dysfunction, and injury[10]and in turn, this increases the risk of unfavourable health outcomes like cancer and cardiovascular disease.[11]

Ubiquinone-10, (also known as coenzyme Q10 or CoQ10) is a lipid-soluble benzoquinone with a side chain containing 10 isoprenyl units. Ubiquinone exists in its reduced form (ubiquinol), which functions as an antioxidant. Small amounts of ubiquinone are produced both endogenously and naturally in a variety of foods, including fish and meat.[12] It is a crucial part of the electron transport chain within the adenosine triphosphate (ATP) synthesis machinery.[13] To fully realize ubiquinone's value as a natural treatment for illnesses associated with inflammation, the precise mechanisms involved still need to be elucidated. Ubiquinone controls the gene expression of other molecules involved in the oxidative reduction pathway and provides effective defence against the oxidation of lipid membranes, proteins, and nucleic acids.[14] Additionally, Peroxisome proliferator-activated receptor (PPAR)-mediated anti-inflammatory response is activated by ubiquinone, which can operate as an agonist of PPARs.[15] Ubiquinone's therapeutic effects are linked to its role in scavenging free radicals and suppressing inflammatory signalling pathways by modulating inflammatory expression.[16]

According to a systematic review, the occupationally lead-exposed group had considerably more lead in their blood and inflammatory markers, such as cytokines (IL-4, IL-6, IL-10, and TNF-α), than the control group[17] A correlation between high blood lead levels and a higher than normal level of C-reactive protein (CRP) has been observed by a study performed by Sirivarasai et al.[18] Previous research has shown that taking a ubiquinone supplement can lower levels of circulating CRP, which is produced by the liver and fat cells and is regarded as a biomarker for the severity of systemic inflammation in the body. Ubiquinone also reduces IL-6 and TNF-α mRNA expression in the liver.[19] Ubiquinone is an add-on therapy that has been proven to be useful in the treatment of metabolic illnesses in several randomized controlled trials (RCTs). However, the results of these studies are inconsistent since they used small sample sizes and participants with varying levels of health.[13,20] The current study aims to determine whether there is a link between ubiquinone administration and a reduction in inflammatory markers in populations who work with heavy metals.

MATERIALS AND METHODS

The Research Committee of the College of Pharmacy at the University of Mosul in Iraq has approved the study project. The current investigation was

conducted in Mosul's main industrial areas. The study was conducted from the beginning of May until the end of June 2022.

Study design

This is a randomized, blind, placebo-control, two-month clinical trial. Participants had at least a year of exposure to an industrial environment. Before study initiation, the lead concentrations in the blood of people included in the study were measured and compared with the concentration of lead in the blood of a normal healthy individual.

Subjects

In the current study, 76 people were evaluated for their suitability to participate, but only 61 of them agreed to participate; the others were excluded because they did not meet the inclusion and exclusion criteria. They have held a variety of jobs with a high risk of heavy metal exposure. These included those who worked as painters, gas station and local generator workers, and car repairers. They ranged in age from 18 to 75 years. They were split into two groups randomly. During the follow-up period, three participants withdrew from the study (Figure 1). In addition to the study participants, five normal individuals who work as farmers were considered as a control to confirm the occurrence of bioaccumulation of lead in subjects included in the study.

Data collection and specimen

Name, age, drinking and smoking habits, time spent working in an industrial area, and contact information were acquired directly from the participant. The concentrations of tumour necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) were measured by suitable laboratory tests for participants before and after the study. The concentration of lead was measured for all candidates before confirming their inclusion in the study, in addition to measuring it in the control group.

Each participant in this study gave 3 ml of venous blood, these samples were drawn in the morning. The blood sample was transferred to vacutest (gel) tubes. By leaving the collected blood at room temperature for two hours, it can coagulate. The coagulated blood is then centrifuged for 15 minutes at a speed of 3000 rpm to obtain the serum. This procedure is repeated after two months to get a second sample.

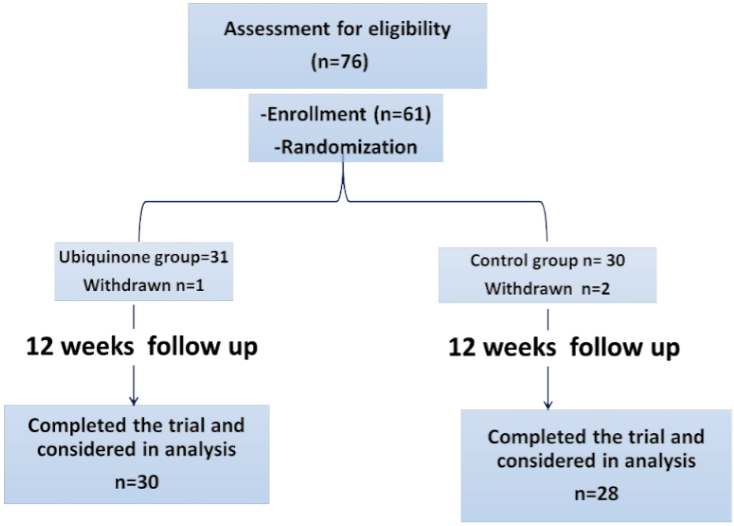

Figure 1 *Patient flow diagram of the study*

Blinding and Compliance

Following the registration of volunteers and receiving their approval to take part in the study, the names of the volunteers were separated at random into two groups, 31 in the ubiquinone group and 30 in the placebo group. The ubiquinone group took the coenzyme CoQ-10®, a product of the NATROL® company in the United States, at a dose of 200 mg per day for two months; while the placebo group took starch-containing pills, administered daily for two months. To ensure blindness, Q10 and starch were placed in the same container. Treatment side effects were evaluated using self-reported questionnaires. In this study, compliance assessment was done by counting tablets.

Inclusion and Exclusion criteria

Men who worked in a variety of industrial professions and were exposed to occupational lead meet the inclusion criteria. These included people working in the industrial area of Mosul city. Their ages were between 18 and 75. Car repair, gas station and local generator workers, and painters were among the jobs included. Those people have lead accumulated in their blood, and the concentrations of lead in their bodies are significantly higher than the average Bioaccumulation of lead in participating individuals was confirmed statistically since the concentrations of lead in the blood of each participant were compared with the average lead concentration of normal control, and subjects with significantly higher lead concentrations in their blood were included in the study.

Where the exclusion criteria include women, males who are under 18 years old, over 75 years old, alcoholics, people who have worked in an industrial field for less than a year, who have a lead concentration in their blood with no significant difference compared to the control group, or other

jobs that do not significantly expose workers to industrial pollutants are excluded from inclusion as professions. All volunteers are working in Mosul's industrial regions. Patients with diabetes, renal failure, neurological illnesses (Parkinson's disease, epilepsy, and essential tremor), stroke, gastrointestinal problems (chronic diarrhoea and inflammatory bowel diseases), and renal failure were also excluded from the trial.

Laboratory Test

Lead concentration was measured by atomic absorption spectrophotometry according to the manufacturer's instructions manual. The inflammatory biomarker high-sensitivity C-reactive protein (hs-CRP) was measured using a turbidimetric immunoassay kit from LDN Co., Germany, and plasma levels of TNF-α and IL-6 were assessed using an ELISA kit from Boster Biological Technology Co., Wuhan, China.

RESULTS

The study included 61 men, all of whom received 200 mg of ubiquinone supplements for two months and were considered the ubiquinone group, while the other 30 received starch-containing tablets and were considered the placebo group. All of these events occurred at random after the participants' acceptance and important information was filled out. After two months of study, one participant from the ubiquinone group and two from the placebo group were dropped, so the total number of participants in the ubiquinone group and placebo group is 30 and 28, respectively.

Demographic characteristics

All participants were males, and they showed an age difference with 55% of them being older than 40 years, as shown in Table 1. Also, there was a difference in the participants' jobs in that about half of them worked in a gas station, and the others were equally distributed between working for local generators, car mechanics, and painters. Another important difference between participants was the duration of time they spent in these jobs, with 43% of them spending less than five years in their current jobs, 35% spending between five and ten years in their jobs, and 25% spending more than ten years in their jobs. Another characteristic of participants was their smoking habit: 40% of them smoke 10-20 cigarettes per day, while 33% smoke more than 20 cigarettes per day.

The pre-study results for participants and the normal control group show that the concentration of lead in the study's included groups was significantly higher than in a normal individual, with a p-value less than 0.05 in all workers exposed to occupational lead

Table 1 *Demographic parameters for the studied groups*

Demographic parameters		Control (n=28)	Ubiquinone (n=30)
Age (years)	<20	2	3
	20-30	4	5
	30-40	5	7
	>40	17	15
Jobs	Car repairing	5	6
	Gas station	12	10
	Local generators	5	7
	Painting	6	7
Duration of work (years)	<5	11	14
	5-10	12	9
	>10	5	7
Number of cigarette per day	No smoking	3	5
	<10	4	4
	10-20	11	12
	>20	10	9

Table 1 *Demographic parameters for the studied groups*

Table 2 *The concentration of lead in the blood of participants compared to that of normal individuals*

Parameters	Control group farmers	Painter	Gas station workers	Local generators workers	Car repairers
Mean(µg/100ml)	2.72	7.06	7.44	7.80	6.83
SD	0.90	2.12	2.23	3.25	1.84
Max	3.76	9.07	9.65	11.63	9.14
Min	1.68	4.17	4.35	4.25	4.36
***p*-value**	-	*0.004*	*0.000*	*0.015*	*0.000*

Table 3 *Percentage of compliance of study participants*

Percentage of compliance	Control (n=28)	Ubiquinone (n=30)
less than 85%	7.14%	3.3%
90% -85%	10.7%	6.7%
90%-95%	39.3%	30.0%
more than 95%	42.9%	60.0%

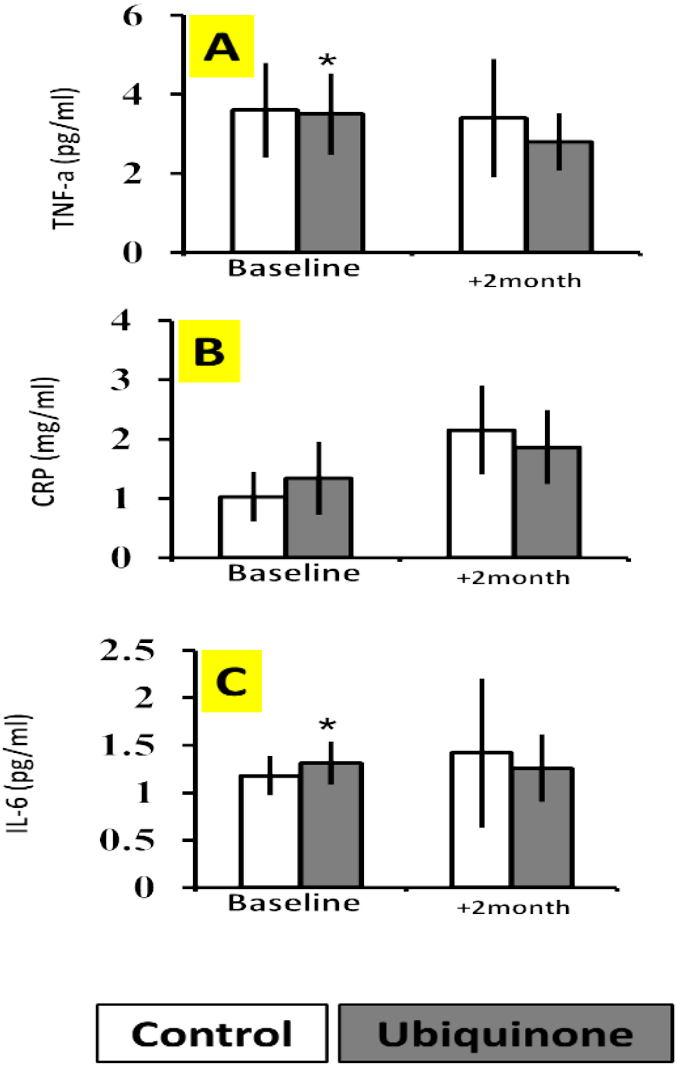

Figure 2 *Ubiquinone slightly reduced pro-inflammatory markers after 2 months of therapy in workplace lead-exposed individuals. Data expressed as mean ± SD, n=58, *P<0.05, * significantly higher as compared to ubiquinone group after 2 months of therapy.*

exposure. The concentration of lead in various participants according to their occupation, along with a p-value comparison to the control group (Table 2). It is worth mentioning that the World Health Organization has set a lead guideline limit of 1µg/100ml.

Participants tolerated ubiquinone supplements well, with no unobserved side effects, and the ubiquinone group's compliance was measured by counting the tablets that remained at the end of the study. Table 3 shows the compliance of the ubiquinone group with their supplement tablet during the study period. Compliance in the ubiquinone group was less than 85% in 3.3% of participants, but the majority of patients have excellent compliance.

There was a significant positive correlation in TNF-α concentration after two months of using ubiquinone supplements, with a decrease of about 0.6 pg/mL (p=0.05), whereas the TNF-α concentration in the placebo group was unchanged (Figure 2A).

The results found a non-significant decrease in CRP in the ubiquinone group after two months of using a ubiquinone supplement that is about 0.3 mg/L (p-value = 0.078). Also in the placebo group, there was a non-significant reduction in CRP concentration (Figure 2B).

The results revealed a significant decrease in IL-6 in the ubiquinone group after two months of using a 0.16 pg/mL ubiquinone supplement (p-value 0.05). While in the placebo group, there was a comparable increase in IL-6 concentration (Figure 2C).

DISCUSSION

Lead was the biomarker utilized to evaluate the degree of heavy metals exposure. The lead concentration in the blood of participants from variable occupations was measured at the start of the study. The study discovered significant increases in lead concentrations in workers in these occupations. Similar results were observed by Singh et al(2022), who found that workers in heavy metals-related occupations have a higher-than-normal level of lead in their blood.[21] Additionally, Muller et al[22] discovered significant increases in lead concentrations in workers in the plating industry.

Ubiquinone is a biologically active substance that regulates gene expression, is a natural antioxidant, and serves as a vital cofactor in the cellular metabolic pathway. The justification for its usage as a dietary supplement and in medical settings is based on these functions.[13,23]Therefore, many studies were conducted for a more comprehensive understanding of the effects of ubiquinone on inflammatory markers. An earlier study discovered that Ubiquinone lowers CRP levels by reducing hepatic mRNA expression of IL-6 and TNF-α. Ubiquinone is effective in several randomized controlled trials for metabolic illnesses.[24]

There was a statistically significant improvement in TNF-α concentration after two months of ubiquinone supplementation in the current study. Although it was higher in the placebo group than in the ubiquinone group at the start of the study, the TNF-α value in the placebo group did not change after two months of ubiquinone supplementation.

This is similar to the results of a meta-analysis study conducted by Zhai et al on nine randomized clinical trials with different dosage forms of ubiquinone supplements and for different durations of ubiquinone supplementation. Three of the clinical trials measured plasma TNF-α levels. Patients with metabolic illnesses who took ubiquinone supplements had significantly lower levels of TNF-α than those who took a placebo, according to the review.[23]

Other meta-analysis studies that support our findings include Farsi et al and Fan et al, who discovered that oral ubiquinone supplementation was significantly effective in lowering serum TNF-α p levels.[25,26]

The effects of inflammatory markers have been studied in patients with different clinical conditions. To begin, Abdollahzad et al observed ubiquinone effects in reducing TNF-α overproduction in an RCT on 44 rheumatoid arthritis patients.[27] Similarly, administration of ubiquinone to patients with multiple sclerosis has resulted in that significant decrease in TNF-α in the intervention group compared to placebo group.[28] These beneficial effects of ubiquinone on TNF-α levels were also observed in patients with multiple sclerosis who received ubiquinone supplementation.[28] In addition to investigating its impact on migraine patients, which yielded comparable results with significant improvement in TNF-α levels.[29]

In contrast to Gokbel et al's study, 100 mg/day ubiquinone administration has shown no effects on TNF-α levels in healthy volunteers. This is most likely due to normal TNF-α levels at the start of the study or an insufficient ubiquinone supplement dosage.[30] Another study published by Raygan et al found that patients with metabolic syndrome who took 100 mg/day of ubiquinone for eight weeks experienced no change in their inflammatory markers. According to the study, the trial design, length, and ubiquinone supplement affect this outcome.[31]

The results of the current study show a statistically non-significant reduction in CRP level of about 0.3 mg/L in the ubiquinone group after using CoQ10 supplementation for two months, while in, the placebo group there is an elevation in CRP level during the study period. Lee et al[32] did not observe an association between the level of high-sensitivity CRP and ubiquinone intake in those suffering from coronary artery disorders.[31] This finding disagrees with a study performed in Iran by Taghizadeh et al, which observed a significant relationship between CRP level and ubiquinone supplementation in 22 polycystic ovarian women who took 200 mg of CoQ10 for eight weeks in an RCT.[33]

Similar findings were observed by Farsi et al, who conducted a study on 20 nonalcoholic fatty liver disease patients by examining IL-6 levels before and after three months of 100 mg CoQ10 supplementation.[25] These studies' substantial CRP reduction may be related to the study subjects' high baseline CRP levels.

This study demonstrates ubiquinone's potent ability to lower IL-6 levels in people exposed to heavy metals. This finding is similar to the results of a meta-analysis conducted by Fan et al.[26] Other RCTs with similar findings, such as Bagheri Nesami et al[34], examined the correlation between CoQ10 supplementation and plasma IL-6 levels in 30 hypertensive patients and compared it to a similar number of patients who received a placebo. Their results indicated that ubiquinone results in a statistically significant improvement of IL-6. On the other hand, studies performed by Gokbel et al[30] and Farsi et al[25] found no correlation between CoQ10

supplementation and plasma IL-6 level, this endogenous response to occupational heavy metal exposure could be explained in the context of cellular response to the surrounding milieu whether being irritant, such as metal or even changes in oxygen levels,[35,36]or due to presence of other underlying diseases.[37,38]

CONCLUSION

This clinical study found that taking 200 mg of ubiquinone daily for two months reduced TNF-α and IL-6 levels in people exposed to heavy metals but had no effect on CRP levels.

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