

# Prophylactic effects of Q10 capsule on proteinuria in diabetic patients

*Efectos profilácticos de la cápsula Q10 sobre la proteinuria en pacientes diabéticos*

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## Abstract

**D**iabetic nephropathy is the most common cause of end stage renal failure in the world. Rigid control of blood pressure and blood sugar is effective in preventing the onset and progression of the disease. But an effective method of preventing it has not yet been identified. Coenzyme Q10 is effective in controlling oxidative stress, glycemic control, and blood pressure. Therefore, its capacity for preventing diabetic nephropathy can be investigated.

In this double blind randomized clinical trial, 68 eligible diabetic patients with normoalbuminuria or microalbuminuria were randomly selected and were divided to two matched groups of 34 by tossing coin. In both groups, fasting blood sugar, 2-hour post prandial glucose, HbA1C, albumin to urinary creatinine ratio (Alb/Cr), and diastolic and systolic blood pressure were measured. One group received 100 mg Q10 daily for 8 weeks and the other group received 8 weeks of placebo. Both groups were monitored and examined every 3 months and finally after 18 months, the variables were again measured by the same initial method and the results were compared with t-test and repeated measure analysis. The Q10 capsule was able to significantly reduce fasting blood glucose, 2h post prandial glucose, HbA1C, and albumin / urinary creatinine ratio (proteinuria) ( $p \leq 0.05$ ), but did not significantly change systolic and diastolic blood pressure.

In this 18-month follow-up, Q10 showed prophylactic effects on glycemic control and proteinuria.

**Keywords:** Diabetic nephropathy, proteinuria, Coenzyme Q10, Q10 capsule.

## Resumen

**L**a nefropatía diabética es la causa más común de insuficiencia renal en etapa terminal en el mundo. El control rígido de la presión arterial y el azúcar en la sangre es efectivo para prevenir el inicio y la progresión de la enfermedad. Pero un método efectivo para prevenirlo aún no ha sido identificado. La coenzima Q10 es efectiva para controlar el estrés oxidativo, el control glucémico y la presión arterial. Por lo tanto, se puede investigar su capacidad para prevenir la nefropatía diabética.

En este ensayo clínico aleatorio doble ciego, 68 pacientes diabéticos elegibles con normoalbuminuria o microalbuminuria fueron seleccionados al azar y se dividieron en dos grupos de 34 lanzando monedas. En ambos grupos, se midieron el azúcar en sangre en ayunas, glucosa post prandial de 2 horas, HbA1C, relación albúmina a creatinina urinaria (Alb / Cr) y presión arterial diastólica y sistólica. Un grupo recibió 100 mg de Q10 diariamente durante 8 semanas y el otro grupo recibió 8 semanas de placebo. Ambos grupos fueron monitoreados y evaluados cada 3 meses y, finalmente, después de 18 meses, las variables se midieron nuevamente por el mismo método inicial y los resultados se compararon con la prueba t y el análisis de medida repetida. La cápsula Q10 fue capaz de reducir significativamente la glucemia en ayunas, la glucosa 2 horas después de la prandia, la HbA1C y la relación albúmina / creatinina urinaria (proteinuria) ( $p \leq 0.05$ ), pero no modificó significativamente la presión arterial sistólica y diastólica.

En este seguimiento de 18 meses, Q10 mostró efectos profilácticos sobre el control glucémico y la proteinuria.

**Palabras clave:** Nefropatía diabética, proteinuria, Coenzima Q10, cápsula Q10.

The World Health Organization (WHO) has reported diabetes as the most common endocrine disorder that accounts for 4 million deaths annually in the world. According to the World Health Organization and the World Association of Diabetes, it is estimated that by the year 2025 there will be more than 300 million diabetic patients in the world and by the year 2035 this will reach to 592 million<sup>1</sup>.

Diabetes Mellitus is associated with multiple complications such as diabetic nephropathy. Diabetic nephropathy develops in about one-third of diabetic patients and is characterized by increased protein and albumin excretion through urine, high blood pressure, and decreased kidney functions. This phenomenon develops over the years. Patients with nephropathy are at increased risk of other complications of diabetes, such as cardiovascular disease, retinopathy and neuropathy<sup>2</sup>.

Generally, 10 to 15 years after the diagnosis of diabetes, microalbuminuria (20 to 200 micrograms per minute or 30 to 300 mg per 24 hours) is appears. Early treatment and attention to quality of life, prevent the progression of microalbuminuria to macrolabineuria and ultimately the renal end stage. As a result, screening and preventing patients as early as possible in the microalbuminuria stage is crucial<sup>3,4</sup>.

Proteinuria screening should be performed annually in all patients immediately after diagnosis of type 2 diabetes and five years after the diagnosis of type 1 diabetes. The easiest screening method for microalbuminuria is to measure the ratio of albumin to creatinine in randomized urine specimens. This measure is largely consistent with 24-hour urine protein estimation<sup>5</sup>.

In type 2 diabetes, due to hyperglycemia, production of free oxygen radicals, weakenes of antioxidant system in the body, altered balance between antioxidant defense, and production of reactive oxygen variants an increase in oxidative stress leads to an increase in oxidative stress<sup>6,7</sup>. Oxidative stress, with increased oxidants and reduction of antioxidants is associated with the pathogenesis of various diseases, such as albuminuria and ultimately diabetic nephropathy<sup>8</sup>.

Several studies in diabetic patients have shown a significant relationship between urinary albumin and oxidation. Q10 is a potent fat-soluble antioxidant that its reduction plays a main role in many diseases such as diabetes, hypertension, and cardiovascular disease. This coenzyme with antioxidant propertes, has an oxidative stress reduction potential and increases antioxidant activity in patients with type 2 diabetes<sup>9-14</sup>.

It is supported by numerous studies<sup>15-18</sup> that Coenzyme Q10 (CoQ10) is a non-enzymatic antioxidant that is also synthesized in the body and plays a vital role in the mitochondrial electron transfer chain, and it also has the potential to regenerate other antioxidants. Therefore, the use of external sources of Q10 in diabetic patients can improve oxidative stress functions, mitochondrial function and glycemic control. Q10 has led to a decrease in biochemical parameters in rats<sup>19</sup>, insulin resistance, as well as an increase in total antioxidant capacity, serum glutathione levels and insulin sensitivity<sup>20</sup> and has decreased blood pressure<sup>21</sup> in recent years. All in all, this study was designed and implemented to determine the effect of Q10 capsule on prevention of proteinuria in diabetic patients.

In this double-blind randomized clinical trial, with registered clinical trial code of IRCT20160408027278N1, based on the prevalence of 20-30% of microalbuminuria with the mean of 190 µg urine albumin in diabetic patients<sup>22</sup>, confidence interval (CI) of 95%, power of 80%, and 35 µg difference based on statistical relation of comparison of the means, 72 diabetic patients with normo albuminuria or microalbuminuria were selected by simple sampling and were randomly divided into two groups of 36 cases based on coin tossing. Each and every patient were mached for some confounding or interfering variables such as age, sex, duration of disease body mass index and comrbidity.

The benefits and potential risks of the intervention were explained to each patient and his/her companion.

After obtaining written well-informed consent, patients' demographic information and laboratory information including fasting blood sugars, post prandial glucose, HbA1C, blood urea nitrogen, serum creatinine, creatinine and urine albumin were measured and recorded in the same laboratory with the same method.

Neither the physicians nor the patients were aware of group allocation. Criteria for inclusion in this study were diagnosis and selection of patients as Type II Outpatient diabetic patients by professors of Diabetes department of Imam Reza clinic, aged 18-60 years old, diabetic patients with normoalbuminuria or microalbuminuria, and an active case in diabetes clinics.

Exclusion criteria were patients with severe physical activity, dehydrated, any type of bleeding, febrile illnesses, type 1 diabetes, record of non-diabetic proteinuria or massive proteinuria, nephrotic syndrome, any malignancy, vasculitis, macroalbuminuria, use of effective drugs in controlling proteinuria, and patients with incomplete diabetes control data.

The intervention group received a pure capsule of Q10, 100 mg daily (American Health Burst pharmaceutical company) for 8 weeks and the other group received placebo capsule (Osveh pharmaceutical company), 100 mg daily for 8 weeks.

During this 8-week period, both groups were monitored by telephone and monthly visits for their use of medications, diet, physical activity, and how Q10 capsules were taken and its possible side effects. Then, both groups were followed for 18 months and during this period they received similar care and diagnostic and therapeutic services every 3 months.

After 18 months, levels of fasting blood glucose, post prandial glucose, HbA1C, serum creatinine, creatinine and urine albumin were measured again in the same laboratory and in the same technique.

In all patients, determination of proteinuria was calculated base on albumin to creatinine ratio in randomly urine sample (morning midstream urine). All patients were advised not to have heavy activity 24 hours before the urine sampling. For UACR test (Urine Albumin (mg)/ Creatinin ratio (g)), a urine sample is collected randomly and its albumin levels to creatinine ratio is measured and the test is reported in mg /g.

In this method, an immunologic method, in which a Monoclonal Antibody is used against Albumin, was applied to measure albumin in primary experiments. Therefore, in the second measurement, the same experimental method was used. The sensitivity of this method in evaluation of 24-hour urine protein is declared to be 85%-87% and its specificity 88%<sup>23</sup>.

Finally, after data collection and entering it into the SPSS 19 software, the two groups were compared by drawing tables and charts and using statistical methods of independent T-test, paired T-test, or its nonparametric equivalents.

## Results

**D**uring the 18 months' follow-up, two patients in intervention and two patients in control group were excluded from the study due to death, migration, or reluctance to continue the treatment.

In 68 patients, 39 (57.3%) were male and 29 (42.7%) were female. At the beginning of the study, the two groups were matched according to the anthropometric and demographic variables according to Table 1, and based on the independent t-test ( $P \geq 0.05$ ).

**Table 1: Comparison of anthropometric, demographic laboratory indices in the beginning of the study and**

variable	group	count	min	max	mean	standard deviation	P value
Age	Q10	34	40	64	60.2	11.4	0.238
	Plasebo	34	43	57	54.3	9.6	
Weight	Q10	34	56	84	70.5	7.0	0.301
	Plasebo	34	58	79	69.4	6.9	
Systolic blood pressure	Q10	34	110	184	143.2	14.3	0.311
	Plasebo	34	100	162	130.4	11.8	
Diastolic blood pressure	Q10	34	58	110	75.6	10.5	0.439
	Plasebo	34	64	105	82.1	8.9	
Fasting blood glucose	Q10	34	76	220	146.9	30.4	0.729
	Plasebo	34	70	204	138.2	25.5	
Post prandial glucose	Q10	34	139	259	196.2	27.4	0.541
	Plasebo	34	153	268	185.6	27.2	
HBA1C	Q10	34	6.1	8.5	7.4	0.72	0.393
	Plasebo	34	6.0	8.1	7.2	0.78	

The distribution of microalbuminuria and normoalbuminuria and urinary albumin to creatinine excretion ratio, in both groups were similar at the beginning of the study ( $P \geq 0.05$ ). However, the urine albumin / creatinine ratio (proteinuria) in terms of gender and on the basis of independent t-test was higher in men than in women

After a minimum of 18 months of taking Q10 or placebo, using the same initial method, the variables of the study were re-measured. According to table 2 and based on paired t-test, weight and systolic and diastolic blood pressure did not change significantly in placebo and Q10 after 18 months ( $P \geq 0.05$ ). Also there was no statistical significant change in fasting blood glucose, post prandial glucose and hemoglobin glycosylated levels in placebo group ( $P \geq 0.05$ ), but there was a statistically significant reduction in fasting blood glucose, post prandial glucose and hemoglobin glycosylated levels in Q10 group ( $P \leq 0.05$ ).

**Table 2: Comparison of mean and standard deviation of anthropometric indices before and after in two groups**

variable	group	before	18 month later	P value
Weight	Q10	70.5±7	71.4 ± 6.3	0.439
	Plasebo	69.4±6.9	69.9 ± 7.8	0.591
Systolic blood pressure	Q10	143.2±14.3	124.7 ± 11.7	0.569
	Plasebo	130.4±11.8	137.6 ± 10.6	0.391
Diastolic blood pressure	Q10	75.6±10.5	81.1 ± 7.8	0.348
	Plasebo	82.2±8.9	78.1 ± 7.9	0.422
Fasting blood glucose	Q10	146.9±30.4	128.1 ± 27.9	0.021
	Plasebo	138.2±25.2	149.8 ± 26.1	0.081
Post prandial glucose	Q10	196.3±27.4	161.1 ± 21.3	0.001
	Plasebo	185.4±27.2	192.1 ± 25.9	0.601
HBA1C	Q10	7.4±0.72	6.0 ± 0.54	0.001
	Plasebo	7.2±0.78	6.9 ± 0.83	0.311

According to Table 3, the proteinuria rate (based on the measurement of albumin to creatinine ratio) was also lower in the Q10 group than in the placebo group after 18 months.

**Table 3: Urine Albumin / creatinine ratio in both groups before and after the study**

variable	group	before	18 month later	P value
Urine alb/ cr	Q10	136.3±34.9	108.5±23.4	0.001
	Plasebo	132.9±36.8	128.3±26.6	0.081
P value		0.231	0.019	

According to Table 4, the proportion of Normo Albuminuria after 18 months was increased in the Q10 group based on the Chi-square test ( $P \leq 0.05$ ). Based on the same test, the relative frequency of microalbuminuria was also lower in Q10 consumption.

**Table 4: Relative frequency of albuminuria and microalbuminuria in the initial stage and 18 months later**

variable	group	Before Count(%)	18 month later Count(%)	P value
Normoalbuminuria (0-25 mg/g)	Q10	11(32.3%)	15(44.1%)	0.001
	Plasebo	13(38.2%)	10( 29.4%)	0.091
Microalbuminuria (25-200mg/g)	Q10	23(67.7%)	19( 55.9%)	0.001
	Plasebo	21(61.8%)	24( 70.6%)	0.228

**A**t the beginning of this study, the mean protein excretion in diabetic men was higher than that of women, and the daily consumption of one Q10 capsule for 8 weeks over a period of 18 months led to a significant reduction in urinary protein excretion. Also, it increased cases of Normo albuminuria, decreased microalbuminuria, and improved glycemic control (fasting blood glucose, post prandial glucose, and HbA1C hemoglobin levels). While the drug did not have any preventive and controlling effect on weight, systolic blood pressure and diastolic blood pressure.

The progression rate to end stage renal disease (ESRD) after nephropathy in men is more than that of women, and men have higher rates of dialysis and transplantation due to diabetes<sup>24</sup>. In the present study, more protein excretion in men is support to fact.

The mean age, weight, duration of diabetes, glycosylated hemoglobin and hypertension were recognized as independent variables that determined albuminuria<sup>22</sup>. In this study, these variables were matched to eliminate their confounding effect.

Few epidemiologic studies have assessed some of the correlation of coenzyme Q10 supplementation with glycemic control. For example, in a study by Singh et al., Supple-

mentation with 60 mg coenzyme Q10 twice daily for 28 days resulted in a decrease in fasting blood glucose<sup>25</sup>. In the study of Zahedi et al., prescription of Q10, led to improved glycemic control. However, no significant changes were made in the lipid profile, which was justified by the low Q10 influence on blood pressure control<sup>26</sup>.

In a study by Abutorabi, the levels of HbA1c and fasting blood glucose were significantly decreased after Q10 consumption. However, lipids and creatinine did not change significantly<sup>27</sup>. In another study, supplementation with coenzymetone with a dose of 75 mg in combination with oral antidiabetic drugs, after 8 weeks, fasting blood glucose and hemoglobin glycosylated were significantly decreased<sup>28</sup>. The results of all these changes are in line with our findings.

In a double-blind clinical trial, the effect of Q10 capsule on hematostase, glucose, lipid profiles, inflammatory markers and oxidative stress in patients with metabolic syndrome (Mets) in 2015 was investigated. There was a significant decrease in resistance to insulin, significant increase in serum total antioxidant capacity, significant increase in serum glutathione and insulin sensitivity, and significant decrease in serum MDA (malondialdehyde) (20). Therefore, glycemic control is expected to improve.

In another study in 2015, the administration of Q10 for 8 weeks with a daily dose of 200 mg resulted in a significant decrease in malondialdehyde (lipid peroxidation index), but the serum HbA1C, FBS and serum adiponectin did not differ significantly between the two groups<sup>29</sup>. The reason for this difference may be explained during the follow up period. On the other hand, in this study, blood pressure was measured immediately after 8 weeks of intervention, and mostly therapeutic goals were sought. While our study has been tracking for 18 months and more preventative effects.

Evidence suggests that people with type 2 diabetes are more sensitive to oxidative stress than others<sup>30</sup>. Oxidative stress and hyperglycemia seem to be causally related. Oxidative stress, in addition to having roots in hyperglycemia, insulin resistance, and functional disorder of the pancreatic beta cells, leads to these conditions. The exact mechanism of how oxidative stress affects hyperinsulinemia is not yet known.

Pancreatic beta cells are very susceptible to damage due to their low enzymatic and antioxidant system. Coenzyme Q10 is also part of the pancreas beta cell and liver. Therefore, Coenzyme Q10 treatment can have a protective effect on pancreatic beta cells, liver, and endothelial, and ultimately improves cell metabolism and insulin function<sup>31,32</sup>.

On the other hand, this quasi-vitamin-like compound, which is similar to vitamin K, has three known biological functions. This compound leads to an increase in mitochondrial adenosine triphosphate (ATP), produces antioxidant effects and enhances the cell membrane's stability<sup>33</sup>.

With all these mechanisms, glycemic control is expected to improve in diabetic patients with Q10.

Coenzyme Q10 supplements can also improve cardiovascular and hypertension and have a protective effect on heart and blood vessels. Researchers have found that supplementation with coenzyme Q10 in people with uncontrolled blood pressure results in a significant reduction in blood pressure. In a study of 76 patients with systolic blood pressure, a significant reduction in systolic blood pressure of 18 mmHg was observed. Coenzyme Q10 also improved the endothelial function of large blood vessels<sup>34</sup>.

In another study, the effect of phenofibrate and 200 mg Q10 in type 2 diabetic patients with abnormal left ventricular diastolic function was investigated. These two interventions, in the form of synergistic, reduced the 24-hour systolic blood pressure, especially during sleep. Q10 also reduced diastolic blood pressure at awakening (35). In addition, the results of the 120-mg Q10 supplementation in patients with primary hypertension and coronary artery disease showed a significant decrease in systolic and diastolic blood pressure<sup>10</sup>. Conversely, the findings from a number of studies indicate that Q10 has no effect on blood pressure<sup>8,12,13</sup>.

The mechanism of Q10 in reducing hypertension is still uncertain. However, there are several theories in this case<sup>11</sup>. The main function of this coenzyme in clinical hypertension is vascular dilatation through direct effects on endothelium and smooth muscle, which reduces environmental resistance<sup>14</sup>.

Another theory is that Q10 reduces environmental resistance by protecting nitric oxide. In some types of blood pressure, superoxide radicals inactivate production of high amounts of nitric oxide. Q10 with its antioxidant effects, may prevent the activation of nitric oxide by these radicals<sup>15</sup>. It is also possible that Q10 may be effective in lowering blood pressure by reducing the viscosity of the blood and lowering the secretion of aldosterone<sup>11</sup>.

All of the above issues have been suggested with probability and by hypothesis, and although Q10 consumption generally leads to lower blood pressure and especially systolic pressure, the preventive effects were not confirmed in this study. For some of its possible reasons, the difference between therapeutic and prophylactic effects can be mentioned. Because variables such as systolic and diastolic blood pressure will not always be constant over time, it is hypothesized that although Q10 is expected to lead to a reduction in systolic and diastolic blood pressure in the short term, its 8-week use and its discontinuous use have no prophylactic effects on blood pressure.

## Conclusions

**P**rescription of co-enzyme Q10 at a daily dose of 100 mg for 8 weeks, by the use of a mechanism for improving the function of beta cells and glucose metabolism and fatty acids, and protective effect on pancreatic beta cells, liver and endothelial, is able to reduce proteinuria in diabetic nephropathy in both males and females. But there is no prophylactic effect on systolic and diastolic blood pressure.

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