The protective effect of coenzyme Q10 on nephropathy in Alloxan-induced diabetic rats

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Abstract
Considering the various effects of Q10 especially hypoglycemic and antioxidant characteristics, it is assumed that Q10 can decrease diabetes nephropathy complications. The present study was conducted in order to evaluate the protective effects of Q10 on serum levels of renal function indicators in diabetic rats induced by alloxan. The experimental model of diabetes type A in rats was induced by intraperitoneally injection of 120 mg Alloxan monohydrate per kg/bw. Q10 treatment group received 75 mg/kg Q10 via gavage for one month and the rats were induced to become diabetic when they received 75 mg/kg Q10 by gavage. From the results it can be concluded that the Q10 administration in diabetic groups can’t be effective as a hypoglycemic, but on the other hand the morphological results of renal capsule thickness suggest that the fibroblastic cells have diabetic reactions following the effects of free radicals; so, by the administration of Q10 the pathogenic reaction can be prevented.

Keywords: Alloxan, Q10, nephropathy, rat, diabetes, hypoglycemic and fibroblastic

Introduction
Being the most common type of diabetes, type I Diabetes has been always as an increasing problem in worldwide health. Although the pathogenesis of type I diabetes is not clear, perfectly, glucose and fat metabolism are involved in the problem (McGarry, 1992). There are most evidences suggesting its oxidative stress role and following it the production of free radicals in diabetic people and their involvement in diabetes pathogenesis (Kaneto et al., 2007). It has been clear that hyperglycemia causes increased active oxygen and leads to severe oxidative tensions in cells (Signorini et al., 2002). The researches have been demonstrated that free radicals removing enzymatic and non-enzymatic defensive systems are attenuated in diabetic people and the lipid peroxidation rate increases in cells (Wohaib et al., 1987). Accordingly, several damages occur in different organs of diabetic people; such that, renal failure has been known as a main factor of diabetics mortality (Pickup et al., 1997). Significant improvement has been obtained in the area of diabetes control using synthetic drugs, but the diabetic people demand to use natural products with anti diabetes characteristics are increasing continuously due to adverse effects of insulin and hypoglycemic medicines (Rao et al., 2007). So, attempts to find natural agents to deal with the disease have an important clinical value. Plants have been used widely and it has been demonstrated that some plants can decrease complications of diabetes with or without decreasing the blood sugar (Neef et al., 1995). There are more than several hundred plant species that have anti diabetic effects. However,
only a few of them have been studied (Noel et al., 1997).

Q10 was discovered in 1957 by Fredrick L. Crane. Q10 is considered as a vitamin or a vitamin-like substance and is found in food resources naturally as other vitamins (Dhanasekaran et al., 2005). Q10 is synthesized in all tissues. Q10 is soluble in fat and found in all cells of the body. It acts as a coenzyme in most enzymatic stages to produce intra cell energy. The maximum amount of it is found in liver, kidney, heart, muscle, and brain. Another function of Q10 is as an antioxidant. Internal synthesis of vitamin and also its absorption through food caused normal rate maintenance of Q10 in a healthy person. The positive effects of Q10 in the treatment of Aids, cancer, gastric ulcers, obesity, muscular dystrophy, sensitivity, immune system function, and body physical strength have been studied (Dhanasekaran et al., 2005). Considering the various effects of Q10 especially hypoglycemic and antioxidant characteristics, it is assumed that Q10 can decrease diabetes nephropathy complications. Due to the antioxidant effects of Q10, it is also assumed that it can decrease the nephropathy side effects of diabetes. In any case, no study has been conducted so far about the Q10 effects on renal tissue damages during of diabetes, the present study was conducted in order to evaluate the protective effects of Q10 on serum levels of renal function in diabetic rats induced by alloxan.

Methods and materials

The experimental model of diabetes type A in rats was induced by intraperitoneally injection of 120 mg Alloxan monohydrate per kg/bw and the serum was used as Alloxan solvent (Ugbenye et al., 2009). 72 hr after injection of Alloxan, glucometer was used to measure the animal FBS using glucometer (Lazos, 1986). FBS within 120 - 250 mg/dl was considered as diabetic in the present study (Gupta et al., 2005). Ziest Chem gluometer kit made by Iran zist chimi was used to measure the parameters.

Control group rats received buffer citrate 0.05 M with pH 4.5 intraperitoneally. The Q10 Treatment group received 75 mg/kg Q10 via gavage for one month (Dhanasekaran et al., 2005). The fourth group (combined experimental group) received 75 mg/kg Q10 by gavage.

At the end of the experimental period, following a 12 hr diet, 20 blood samples were obtained from each group. The data were expressed as Mean±SEM. ANOVA was used for data analysis. P<0.05 was used to determine the significance level.

Results

Histological changes

Based on tissue samples in diabetic group, severe tissue damages were observed. The damages were as acute tubular necrosis, interstitial tubular nephritis, vacuolar nephrosis, fat changes and vascular arteriolesclerosis, which were observed both in the cortex and medulla.

The coagulative necrosis was mainly observed in proximal tubules in a wide range of tissues. The tubules’ cytoplasm inflammation and the decrease of tonality power of the cells along with tubular cells flux were also recorded.

Furthermore, outstanding increase of the mesangial matrix, dilation of the urinary space, as well as visceral and wall adhesions of Bowman's capsule were observed. Hyaline cysts were seen in medullar part of Alloxan-induced rats’ kidneys. Other side effects were renal vascular arteriosclerosis which was observed as hyalination of vessels’ wall along with stenosis.

Mononuclear infiltration in interstitial renal tissue, glomerular congestion, and hemorrhage in the interstitial spaces of tubules were visible in diabetic rats.

Hypertrophy in renal tubules’ epithelial cells in the proximal and distal parts, followed by fatty changes of
the cell cytoplasm was observed as fine and transparent vacuoles around nuclear (vacuolar nephrosis) region.

In the kidneys of Q10-administrated rats all signs were seen as mild. The occurrence of coagulation necrosis of renal cortex and medulla was lower in the experimental group compared with diabetics. Glomerular congestion in Q10 experimental was as diabetics, but the congestion has been decreased in tubules interstitial spaces. Hyaline cysts dispersion in Q10-experimental group was very low. The rate of arteriosclerosis was lower in Q10-experimental group compared with diabetics, such that there was no stenosis.

Visceral and wall adhesions of Bowman’s capsule as well as mononuclear cells infiltration and interstitial space edema and also glomerular capillaries’ microtrombosis were the same in both groups.

**Effect on blood sugar**

The mean blood sugar in normal, Q10, Alloxan, and Q10 + Alloxan groups were 94.8 ± 3.88, 94.2 ± 3.4, 245.1 ± 2.1, and 240.5 ± 9.26 mg/dl, respectively. The obtained results suggest no significant difference between Alloxan and Q10 ± Alloxan groups (P>0.05).

**Effect on Renal capsule thickness**

The mean renal corpuscle thickness in normal, Q10, Alloxan, and Q10 + Alloxan groups were 3.78 ±0.175, 4.33 ± 0.183, 16.57±0.849, and 8±0.527 µm, respectively. The obtained results suggest a meaningful difference between Alloxan and Q10± Alloxan groups (P<0.05).
Table -1. Comparison of the parameters the control and experimental groups. Dissimilar letters in each vertical column indicate a significant difference in Mean + SD, (P<0.05)

<table>
<thead>
<tr>
<th>groups variables</th>
<th>Control</th>
<th>Q10</th>
<th>Alloxan</th>
<th>Q10+Alx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal capsule thickness (µm)</td>
<td>3.87±0.175a</td>
<td>4.33±0.183a</td>
<td>16.57 ±0.849c</td>
<td>8 ±0.527 b</td>
</tr>
<tr>
<td>Renal corpuscle diameter (µm)</td>
<td>108.37±3.77a</td>
<td>108.12±3.47 a</td>
<td>59.16±2.1 a</td>
<td>73.95±2.5 a</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>94.8 ±3.88 a</td>
<td>94.2 ±3.45 a</td>
<td>245.1 ±20.9 b</td>
<td>240.5 ±9.26 b</td>
</tr>
<tr>
<td>Renal weight</td>
<td>1±0.121 a</td>
<td>1±0.145 a</td>
<td>0.74±0.09 b</td>
<td>0.77±0.11 a</td>
</tr>
</tbody>
</table>

Explain : a,b,c

Fig.-4a. Microscopic view of the diabetic rats’ renal medulla and the observation of hyalinated cysts in urinary collecting duct lumen (H&E staining, magnification of 400×). Fig.-4b : Microscopic view of a diabetic rat’s renal cortex. Occurrence of tubular acute coagulant necrosis, increased mesangial matrix, visceral and wall adhesion of Bowman’s capsule, as well as urinary space dilation (H&E staining, magnification of 400×).

Fig.-5. Comparison of Mean ± SEM of blood sugar, followed by administration of Q10, Alloxan, and both of which coincidentally in rats in a one-month period. Dissimilar letters show a significant difference of mean among groups. (P<0.01).

Fig.-6. Comparison of Mean ± SEM of renal capsule thickness followed by administration of Q10, Alloxan, and both of which coincidentally in rats in a one-month period. Dissimilar letters show a significant difference of mean among groups (P<0.05).

**Discussion**

Diabetic nephropathy has been studied by several researchers as an important damage, and it has been always trying to decrease the damages on renal tissue in diabetics all over the world. Different drugs have been used in this area, but they have failed so far to decrease the side effects of diabetes on renal tissue.
Several methods have been suggested in order to study the renal toxicity such as urea and serum creatinine levels, as well as glomerular infiltration (Lau, 1999). In the present study the renal toxicity was examined by histopathologic and morphological studies on renal tissue, such as tubular nephritis, tubular cells flux, and protein casts aggregation especially in the medulla.

In a study conducted by Tabrizi et al. (2011) the increased amount of malondialdehyde in the renal tissue of diabetic rats induced by Alloxan revealed that oxidative stress caused by free radicals is one of the mechanisms involved in diabetic nephropathy.

Oxidative stresses along with increased production of free radicals have a main role in renal pathologic damages. In a study, the diabetes-induced rats with Alloxan had different cell damages along with cell membrane damage which may be due to oxidative stresses resulted by hyperglycemia. Early renal damage in this study is consistent with the results obtained by Liu et al., (2008) and Tabrizi et al., (2011) on diabetic nephropathy. Oxidative stress resulted by super oxide anions are involved in diabetic nephropathy pathophysiology (Vural et al., 2002).

The causes of the tangled tubes following diabetes have not been known yet, but several factors such as semi-insulin growth factor is involved (Flyvbjerg et al., 1990).

The important observed damage in the present study in diabetes-induced rat kidney by Alloxan was in the mesangial matrix. It has been revealed that the increased mesangial matrix in diabetic nephropathy has a relationship with the changes in extracellular matrix (Yamanea et al., 2004). When the blood sugar is very high, the mesangial cell proliferation is stimulated and a high rate of collagen 1 and 4 , as well as TGF-β are produced.

According to the obtained morphological results in the present study it can be said that the Q10 administration in diabetic groups can’t be effective as a hypoglycemic, but on the other hand the morphologic results of renal capsule thickness suggest that the fibroblastic cells have diabetic reactions following the effects of free radicals; so, by the administration of Q10 the pathogenic reactions can be prevented.

Also, according to the obtained results about the renal corpuscle diameter it was revealed that Q10 can prevent meaningfully from the renal corpuscle diameter decrease resulted by free radicals following the diabetes disease.

The effects of Q10 on a damaged kidney suggest its high effects of the anti oxidant factors which can resist against free radicals created by diabetes disease.

The damages which were observed in renal tissue as a result of diabetes disease in the present study are as follows: tubular acute necrosis, interstitial tubular nephrosis, vacuolar nephrosis, fatty changes, and vascular arteriosclerosis; and the administration of Q10 had a mild effect on these damages. Necrosis occurrence in Q10-administrated groups was observed in a lower range. Furthermore, interstitial spaces congestion was decreased by Q10 administration, which suggested the effect of Q10 antioxidants against free radicals. In the present study, it was observed that Q10 administration had not done significant effect on some pathologic cases such as glomerular congestion, capillary thrombosis, and interstitial spaces edema.

Having several anti oxidant factors, Q10 can fight against free radicals resulting out of diabetes, which have irreversible pathogenic effects on the renal tissue.

It is well known that diabetic nephropathy is caused by several factors which are not preventable by hyperglycemia and hypertension control. Although in the early stages of the disease the diabetic nephropathy changes are induced by hyperglycemia, the later injuries have no relationship to hyperglycemia (Liu et al., 2008).

According to the obtained morphological results in the present study it can be said that the Q10 administration in diabetic groups can’t be effective as a hypoglycemic, but on the other hand the morphologic results of renal capsule thickness suggest that the fibroblastic cells have diabetic reactions following the effects of free radicals; so, by the administration of Q10 the pathogenic reactions can be prevented.
Then, blood glucose control is not enough by itself to postpone the process of diabetic nephropathy.

**Conclusion**

In conclusion it can be said that the positive effect of Q10 in a partial recovery from diabetic nephropathy is consistent with the results of our study, such that there is a significant difference between control and treatment groups in terms of resulted damages, like glomerulonephritis, tubular necrosis, and nephrosis. So, it can be concluded that the administration of Q10 can be considered as a preventive procedure of diabetes side effects on kidney.

**References**


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