ORIGINAL ARTICLE

Beneficial effects of co-enzyme Q$_{10}$ and rosiglitazone in fructose-induced metabolic syndrome in rats

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Received 10 April 2012; accepted 7 October 2012
Available online 22 November 2012

Keywords
Rosiglitazone;
Co-enzyme Q$_{10}$;
Leptin;
Tumor necrosis factor;
Insulin resistance

Abstract
Increased fructose consumption is strongly associated with metabolic syndrome (MS). This study was performed to elucidate the role of co-enzyme Q$_{10}$ (CoQ) and/or rosiglitazone (Rosi) in fructose induced MS. Four groups of rats ($n = 8–10$) were fed on fructose-enriched diet (FED) for 16 weeks. One served as FED-control while the remaining groups were treated with CoQ (10 mg/kg/day), Rosi (4 mg/kg/day) or their combination during the last 6 weeks. Another group was fed on normal laboratory chow (normal control). At the end of the experiment, blood samples were collected for estimation of markers related to MS. In addition, histological examination of liver, kidney and pancreas samples was done. Induction of the MS was associated with increased body weight gain (34%) coupled with elevated levels of blood glucose (48%), insulin (86%), insulin resistance (270%), uric acid (69%), urea (155%), creatinine (129%) and blood lipids with different degrees. Fructose-induced MS also reduced plasma catalase (62%) and glutathione peroxidase (89%) activities parallel to increased serum leptin and tumor necrosis factor-alpha (TNF-$\alpha$) levels. These changes were coupled by marked histological changes in the examined tissues. Treatment with CoQ or Rosi attenuated most of MS-induced changes. Besides, the combination of both agents further reduced blood glucose, total cholesterol, triglycerides and urea levels, as well as, normalized serum levels of leptin and TNF-$\alpha$. In addition, combined therapy of both agents elevated HDL-cholesterol level and glutathione peroxidase activity. In conclusion, the present study proves the benefits of co-supplementation of CoQ and Rosi in a fructose-induced model of insulin resistance.

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1. Introduction

The metabolic syndrome (MS) is a constellation of risk factors for cardiovascular disease and type-2 diabetes that consist of abdominal obesity, dyslipidemia, hyperuricemia, $\beta$-cell dysfunction, insulin resistance, and hyperglycemia.$^1$ One of the most important causes that contributes to the growing worldwide prevalence of MS, obesity and type-2 diabetes is the change of dietary habits principally due to the increased intake
of simple sugars, mainly fructose, commonly used in food industry and sugar-sweetened drink. Co-enzyme Q₁₀ (CoQ) is an oil-soluble, vitamin-like substance present in most eukaryotic cells, primarily in the mitochondria. It is a component of the electron transport chain (ETC) and participates in aerobic cellular respiration, generating 95% of human body energy in the form of ATP. CoQ has been reported to lower glycated hemoglobin levels and lipid peroxidation parallel to increasing the level of some antioxidant enzymes in the pancreas of diabetic rats. Furthermore, it has been found that supplementation of CoQ to streptozotocin (STZ)-diabetic rats attenuated most of diabetic-induced changes in oxidative stress.

Rosiglitazone (Rosi) is a highly potent and selective agonist for peroxisome proliferator activated receptor-γ (PPAR-γ). Its primary action is the improvement of insulin sensitivity in the muscles and adipose tissue, as well as, inhibition of hepatic gluconeogenesis.

The present work was therefore carried out to further investigate the possible beneficial role of CoQ in fructose-induced insulin resistance syndrome alone or in combination with Rosi.

2. Materials and Methods

2.1. Drugs and chemicals

CoQ and Rosi were kindly provided as finely dispersible powders by MEPACO Pharmaceutical Company (Egypt) and Memphis Pharmaceutical Company (Egypt), respectively. They were suspended in 1% tween 80 shortly before administration to animals. The concentrations of the drugs were adjusted so that each 100 g of animal’s body received orally 1 ml of either suspension containing the required dose. Fructose was purchased from Elnasr-Pharma, Egypt. Mineral and vitamin mixtures were obtained from Sigma–Aldrich, USA. All other chemicals were of the highest grade commercially available.

2.2. Animals

Male Wistar albino rats, 120–140 g body weight, were purchased from the National Cancer Institute, Cairo, Egypt and left to accommodate in the animal facility of the Faculty of Pharmacy, Cairo University, for 1 week before being subjected to experimentation. All animals were allowed free access to diet and tap water. The study was conducted in accordance with ethical procedures and policies approved by the Ethics Committee of Faculty of Pharmacy, Cairo University.

2.3. Induction of insulin-resistance syndrome

Insulin-resistance was induced by feeding rats a fructose-enriched diet (FED) for 10 weeks according to the method described by Bezerra and coworkers. FED was composed of fructose (660 g/kg), soya protein (200 g/kg), sheep fat (60 g/kg), cellulose (30 g/kg), L-lysine (10 g/kg), choline chloride (10 g/kg), DL-methionine (10 g/kg), mineral mixture (10 g/kg) and vitamin mixture (10 g/kg). Diet was freshly prepared every 3–4 days and stored at 2–8 °C till used.

2.4. Experimental design

Rats were provided with a FED for 10 weeks. Blood samples were collected randomly after 4, 6, 8 and 10 weeks from the initiation of the FED. Serum levels of fasting blood glucose (FBG), triglycerides (TGs) and total cholesterol were estimated to ensure the induction of insulin-resistance syndrome. FED-fed rats were randomly allocated into 4 groups (8–10 rats each). One group served as FED-fed control group, while the other 3 groups were treated orally with CoQ (10 mg/kg/day), Rosi (4 mg/kg/day) or their combination, respectively for 6 weeks. Animals were maintained on the FED during the treatment period. A group of animals consisting of 10 rats was run concurrently and maintained on standard rat chow diet and assigned as the normal-control group. Body weight was recorded once weekly.

By the end of the treatment period, animals were fasted for 12 h and blood samples were withdrawn from the retro-orbital plexus for the estimation of the levels of FBG, insulin, lipids, leptin, tumor necrosis factor-alpha (TNF-α), creatinine, uric acid and urea. In addition, homeostasis model assessment of insulin resistance (HOMA-IR score) as an indicator of insulin resistance and LDL-cholesterol (LDL-C) level were calculated. Plasma activities of catalase and glutathione peroxidase (GSH-Px) enzymes were also estimated as oxidative stress biomarkers. Samples of liver, kidney and pancreas from each group were preserved in 10% formalin prepared in saline and kept for histological examination.

2.5. Determination of biochemical parameters

FBG level (mg/dl) is oxidized enzymatically to yield a red violet quinoneimine that can be determined colorimetrically using a test reagent kit (EMAPOL, Poland); whereas serum insulin level (μIU/ml) was predicted following a solid phase two-site enzyme immunoassay (DRG Instruments GmbH, Germany). The obtained values of both FBG and insulin levels were then used to calculate insulin resistance as described by Matthews et al.

Insulin resistance (HOMA-IR) score

\[
\text{HOMA-IR} = \frac{\text{FBG}(\text{mmol/l}) \times \text{serum insulin(μIU/ml)}}{22.5}
\]

The serum levels of leptin (ng/ml) and TNF-α (pg/ml) were also estimated by solid-phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle using test reagent kits (DRG Instruments, GmbH, Germany) and (ID labs, Canada), respectively.

Total cholesterol (mg/dl) and HDL-C (mg/dl) levels were determined following their hydrolysis and oxidation to yield colored quinoneimine derivatives using test reagent kits (Biodiagnostics, Egypt). TGs level (mg/dl) was estimated by a reagent kit (EMAPOL, Poland), in which TGs were hydrolyzed with lipoprotein lipase to form glycerol, which forms a complex with H₂O₂ giving a colored derivative. The obtained levels of total cholesterol, HDL-C and TGs were then used to calculate the serum level of LDL-C as that described by Friedewald et al.
LDL − C (mg/dl) = Total cholesterol − (HDL − C + \frac{TG}{5}) \tag{2}

Kidney function tests including the levels (mg/dl) of uric acid, urea and creatinine were performed using test reagent kits (Biodiagnostics, Egypt). In addition, the activities of some antioxidant enzymes including catalase (IU/l) and GSH-Px (U/ml) were estimated using test reagent kits (Biodiagnostics, Egypt) and (Cayman, USA), respectively.

2.6. Preparation of sections for histopathological examination

Animals were sacrificed; liver, pancreas and kidney samples of 3–4 rats of each group were isolated immediately. Kidneys were opened along the convex side to insure good fixation and then all samples were fixed in 10% formalin prepared in saline for at least 3 days. Afterward, all the specimens were washed in tap water for half an hour and then dehydrated using ascending grades of alcohol (70%, 80%, 90% and finally absolute alcohol). Specimens were then cleared in xylene and impregnated in soft paraffin wax at 55 °C and embedded in hard paraffin. Sections of 6 μm thickness were cut using a slide microtome then, stained with hematoxylin and cosin \(^12\) for histopathological examination. Images were captured and processed using Adobe Photoshop version 8.

2.7. Statistical analysis

Data were expressed as mean values ± SEM. Comparison between the mean values of different groups was carried out by using one way analysis of variance (ANOVA) followed by Tukey–Kramer post hoc test for multiple comparisons. In all data analysis, \(p \leq 0.05\) was considered significant.

3. Results

3.1. Effect of CoQ and/or Rosi on weight gain

During the experimental period, FED resulted in a gradual increase in body weight starting from the third week after initiation of the diet and continued thereafter. An average weight gain of 56% was reached by the end of the experiment compared to 34% for the normal-control group. Treatment of insulin-resistant rats with Rosi was not associated with any significant change in body weight gain of FED-fed rats; however administration of CoQ and its combination with Rosi reduced the increased body weight gain by 57% and 62%, respectively (Fig. 1).

3.2. Effect of CoQ and/or Rosi on glucose homeostasis, lipid profile, cytokines, kidney function and antioxidant enzymes

The level of FBG was nearly doubled in the serum of FED-control rats. Treatment with CoQ, Rosi and their combination significantly decreased FBG by 39%, 20% and 44%, respectively. At the same time, insulin level was increased in the serum of FED-control rats by nearly 2 folds. Treatment with Rosi alone or combined with CoQ did not affect this increased level, but it was almost normalized by the treatment with CoQ. The increased levels of FBG and insulin of FED-fed rats resulted in nearly a 4-fold rise in the HOMA-IR score. Treatment with CoQ, Rosi or their combination lowered the raised score by approximately 70%, 34% and 43%, respectively (Table 1).

Metabolic syndrome was also associated with a 2-fold increase in serum leptin level. Treatment with the selected agents was accompanied by normalization of this increased level. In addition, the sera of FED-fed rats showed a marked elevation in the level of the pro-inflammatory cytokine, TNF-α, by 125%. Treatment with CoQ, Rosi or their combination significantly decreased the raised level by 73%, 77%, and 78%, respectively (Fig. 2).

Moreover, insulin resistance syndrome was accompanied by marked dyslipidemia as evidenced by the observed increase in the levels of total cholesterol, LDL-C and TGs paralleled to reduction of HDL-C level, which was found to be nearly halved following the FED. Treatment with CoQ resulted in a 40% reduction in TGs level and a 24% elevation in the HDL-C level; however it was not associated with any significant change in the total cholesterol and LDL-C levels. Similarly, treatment of FED-fed rats with Rosi did not result in any marked alteration in FED-induced dyslipidemia. On the other hand, a combined treatment with CoQ and Rosi reduced the elevated total-cholesterol, LDL-C and TGs levels by 34%, 31% and 36%, respectively, paralleled to 123% elevation in the HDL-C level (Fig. 3).

Compromised kidney function was another important aspect of the disease, results of the current study showed that insulin-resistance syndrome was associated with 69% elevation in uric acid level and with 3- and 2-fold increases in serum urea and creatinine levels, respectively. Treatment with CoQ, Rosi and their combination lowered the raised uric acid level by

![Figure 1](image1.png)  
**Figure 1** Effect of 6 weeks of oral treatment with rosiglitazone (Rosi; 4 mg/kg), co-enzyme Q\(_{10}\) (CoQ; 10 mg/kg) or their combination on body weight gain of insulin resistant rats fed for 16 weeks with fructose-enriched diet (FED). Results are expressed as means ± SEM (\(n = 8–10\)). *Significantly different from normal-control group at \(p \leq 0.05\). **Significantly different from FED-control group at \(p \leq 0.05\).
54%, 41% and 23%, respectively. Similarly, the administration of CoQ to FED-fed reduced the elevated urea level by 51%, however the administration of either Rosi alone or in combination with CoQ did not show any significant change in the raised urea level. In the same way, treatment with CoQ and/or Rosi had no effect on the elevated creatinine level (Table 2).

Furthermore, fructose-induced MS was accompanied by a marked oxidative insult as evidenced by the observed 3- and 9-fold reductions in the plasma activities of catalase and GSH-Px. Treatment with CoQ alone resulted in a marked increase in the catalase activity by 108%. On the other hand, CoQ in combination with Rosi almost normalized the reduced GSH-Px activity (Fig. 4).

3.3. Effect of Rosi or CoQ and their combination on histological changes

3.3.1. Liver samples

FED-control rats showed marked dilatation and congestion in the central and portal veins with severe fibrosis extending from
the portal area in between hepatocytes distorting the normal architecture of liver tissue. The hepatocytes showed marked fatty changes and hydropic degeneration in a diffuse manner, an effect that was reversed by the treatment with Rosi. Treatment of insulin resistant rats with CoQ showed marked improvement in the hepatic structure however, hydropic degeneration in the hepatocytes especially in the zone surrounding the portal area was still present. The combination of both agents showed an almost normal hepatic structure. However, few individual hepatocytes still showed some fatty changes (Fig. 5).

3.3.2. Kidney samples

Histopathological examination of renal sections of FED-control rats showed focal hemorrhage with congestion in the cortical blood vessels and degeneration in the lining endothelium of the tubules. Proliferation in the lining endothelium of the glomerular tuft and focal inflammatory cell infiltration in between the tubules was also noticed. Treatment with Rosi alone or in combination with CoQ markedly reduced focal hemorrhage and inflammatory cell infiltration however, congestion in the glomerular tuft was still observed. However, single treatment with CoQ showed vacuolization in the lining endothelium of the congested glomerular tuft associated with focal inflammatory cells’ infiltration. Focal hemorrhage in between the tubules was also noticed (Fig. 5).

3.3.3. Pancreas samples

Pancreatic sections of insulin resistant rats showed marked hypertrophy in the islets of Langerhan’s in a diffuse manner. Fibrosis within the lobules of the pancreas with thickening of the blood vessel walls was observed. Islets of Langerhan’s showed a slight increase in the amount of the connective tissue in between the cells. Treatment with Rosi restored the normal structure of the pancreas however, CoQ alone or in combination with Rosi showed diffuse manner hypertrophy all over the islets of Langerhan’s and the congestion in the lobular blood vessels accompanied by very fine fibrosis among these blood vessels. Cystic dilatation in the ducts of exocrine acini was also observed (Fig. 5).

4. Discussion

MS has become a worldwide health problem. Since, it is difficult for patients to follow a diet and/or exercise regimens that would improve their symptoms, therefore the investigation of agents that may deal with the serious aspects of the disease is an important field of research. Micronutrients such as natural antioxidants have received recently a great deal of attention with respect to their efficacy in treating the insulin-resistance syndrome complications. CoQ is a naturally occurring potent antioxidant with proven efficacy in a wide range of diseases. It has also been shown to lower glycated hemoglobin levels.

<table>
<thead>
<tr>
<th>Normal-control</th>
<th>Fructose-fed (Control)</th>
<th>Rosi (4 mg/kg)</th>
<th>CoQ (10 mg/kg)</th>
<th>Rosi + CoQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid (mg/dl)</td>
<td>2.22 ± 0.13</td>
<td>7.05 ± 0.31*</td>
<td>4.16 ± 0.52*</td>
<td>3.23 ± 0.30*</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>6.94 ± 1.04</td>
<td>17.73 ± 1.17*</td>
<td>16.43 ± 1.06*</td>
<td>8.74 ± 0.59*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.31 ± 0.042</td>
<td>0.71 ± 0.044*</td>
<td>0.73 ± 0.073*</td>
<td>0.63 ± 0.08*</td>
</tr>
</tbody>
</table>

Insulin resistance was induced by feeding rats with fructose enriched diet for 16 weeks. Results are expressed as means ± SEM (n = 8–10).

* Significantly different from normal-control group at p ≤ 0.05.

# Significantly different from fructose-fed group at p ≤ 0.05.

$ Significantly different from Rosi-treated group at p ≤ 0.05.

Table 2 Effect of 6 weeks of daily treatment with rosiglitazone (Rosi), co-enzyme Q₁₀ (CoQ) or their combination on serum uric acid, urea and creatinine, levels of insulin resistant rats.
and lipid peroxidation products while raising the level of some antioxidant enzymes in the pancreas of diabetic rats, suggesting that CoQ may possess protective effects against fructose-induced changes in rats.

In the present study, maintaining rats on FED for 16 weeks was associated with multiple disorders including increased weight gain, hyperglycemia, dyslipidemia, hyperinsulinemia, hyperleptinemia, abdominal obesity, hyperuricemia, oxidative stress and insulin resistance.

Treatment of FED-fed rats with Rosi reduced insulin resistance and hyperglycemia. Moreover, it normalized the elevated leptin level as well as normalized fructose-induced pancreatic histopathological changes. These changes are in accordance with those of Türüner et al. who reported that Rosi was able to reduce plasma leptin concentration. Lustig et al. also reported that reduction of insulinemia improves insulin resistance and leptin sensitivity.

Despite the fact that treatment with Rosi (4 mg/kg/day) reduced the elevated serum leptin level, it maintained the increased body weight gain of FED-fed rats. This finding is quite consistent with that of Loizzo et al. who found that monotherapy with Rosi (8 mg/day) in obese-diabetic patients was associated with insignificant changes in body weight. In addition, Türüner et al. reported that rats treated with Rosi (30 mg/kg/day) gained more weight as compared to their respective controls.

Treatment of insulin-resistant rats with CoQ reduced insulinemia, hyperglycemia, insulin resistance and leptin level. In addition, it significantly decreased body weight gain. In harmony with the present results, Rauscher et al. showed that CoQ supplementation in STZ-diabetic rats attenuated most of diabetic-induced changes. The combination of Rosi and CoQ behaved in the same manner and resulted in a further reduction of insulinemia, hyperglycemia, insulin resistance and leptin level. Furthermore, it markedly reduced body weight gain in FED-fed rats.

Co-enzyme Q10 is an essential part of the cellular machinery used to produce ATP, which provides the energy for muscle contraction and other vital cellular functions. Increased energy production may speed up metabolism and accelerate weight loss as that observed in the current study. Hill et al. reported that blood leptin levels decrease considerably during weight loss with subsequent reduction in the number and size of fat cells, a fact that may explain the observed decline in the elevated serum leptin levels of FED-fed rats treated with CoQ. On the contrary, results of the current study revealed that the treatment of FED-fed rats with CoQ did not show any improvement of FED-induced histopathological changes, a finding that may necessitate further investigation.

Disturbed lipid metabolism is considered as another characteristic feature of MS. The current study shows that supplying rats with FED elevated the levels of TGs, LDL-C and total

Figure 5  Effect of 6 weeks of oral treatment with rosiglitazone (Rosi; 4 mg/kg), co-enzyme Q10 (CoQ; 10 mg/kg) or their combination on structure of different organs isolated from insulin resistant rats. Tissues were stained with hematoxylin and eosin (magnification × 200). (a) Normal hepatic tissue showing polyhedral hepatocytes with eosinophilic cytoplasm and large rounded vesicular nuclei. (b) FED hepatic tissue with marked dilatation and congestion in central and portal veins with fibrosis, fatty changes and hydropic degeneration. (c) Rosi-treated FED-rats with normal hepatic structure. (d) CoQ-treated FED rats showing general hepatic tissue improvement, hydropic degeneration in the hepatocytes especially those surrounding the portal area was still observed. (e) (Rosi + CoQ)-treated FED rats showing normal hepatic appearance but with few individual hepatocytes showing fatty changes. (f) Normal renal tissue showing glomerulus that is located between many tubules. (g) FED renal tissue with focal hemorrhage, congestion in cortical blood vessels and proliferation in lining epithelium. (h) Rosi-treated FED rats with marked improvement in renal tissue, congestion in glomerular tuft still observed. (i) CoQ-treated FED rats showing vacuolization of lining endothelium of the congested glomeruli tuft and focal inflammatory cells infiltration in between the tubules. (j) (Rosi + CoQ)-treated FED rats showing swelling and vacuolization of the endothelial cells lining the glomerular tuft. (k) Normal pancreatic structure showing serous acini located in lobules, which contains islets of Langerhan’s. (l) FED pancreatic tissue with diffuse manner hypertrophy in islets of Langerhan’s with fibrosis in the lobules and thickening in blood vessel walls. (m) Rosi-treated FED rats with normal pancreatic structure. (n) CoQ-treated rats showing diffuse manner hypertrophy all over the islets of Langerhans. (o) (Rosi + CoQ)-treated rats showing congestion in the lobular blood vessels accompanied with very fine fibrosis among these blood vessels and cystic dilatation in the ducts of the exocrine acini.
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cholesterol in serum. These results are in harmony with those of other investigators. On the other hand, HDL-C level was markedly reduced in the serum of FED-fed rats. This finding was in accordance with that of Ohmori et al. who reported a decrease in serum HDL-C after 4-weeks of fructose feeding.

The results of the present study revealed that the treatment of FED-fed rats with Rosi did not show any significant improvement in FED-induced dyslipidemia. This finding is consistent with that of Goldberg et al. who reported that the treatment of patients with type-2 diabetes and dyslipidemia with Rosi was associated with a significant increase in serum levels of TGs, total cholesterol, LDL-C and HDL-C. Similarly, Ko et al. reported that Rosi treatment in type-2 diabetes was associated with a significant increase in serum total cholesterol, HDL-C and LDL-C in comparison to the control group. Recently, it was shown that the addition of Rosi to an existing anti-diabetic medication regimen improves glycemic control to a lesser extent when compared to metformin or sulfonylureas, and may be accompanied by deterioration of patients’ lipid profiles. Similarly, the administration of CoQ to insulin-resistant rats did not show any significant change in the deteriorated lipid profile. In a similar fashion, Kunitomo et al. revealed that CoQ supplementation to genetically induced insulin resistant rats prevented the elevated insulin levels without affecting dyslipidemia.

In contrast to the individual effect of either Rosi or CoQ, the combined treatment of both agents markedly reduced the elevated total cholesterol, LDL-C and TG levels parallel to an elevation in HDL-C level. Several studies documented the potential role of Rosi and CoQ on hypertriglyceridemia in insulin-resistant states. Rosi treatment was shown to improve hypertriglyceridemia by increasing fat oxidation in the muscles and in the liver as well as the redistribution of circulating TGs in the tissue. Regarding the effect of CoQ, Modi et al. reported that the administration of CoQ to STZ-diabetic rats for 4 weeks resulted in a significant decrease in serum TGs level, a finding that is consistent with the present results.

The results of the current study also showed that, the treatment of FED-fed rats with Rosi resulted in normalization of fructose-induced histopathological changes of the liver tissue which included severe congestion together with hydropic degeneration and notable fatty changes in the hepatocytes. Quite consistent with the aforementioned findings, Tahan et al. reported that Rosi attenuated liver inflammation in a rat model of non-alcoholic steatohepatitis. Beneficial effects of Rosi could be explained by its anti-inflammatory effect mediated by the activation of PPARγ on macrophages resulting in a decreased production of the pro-inflammatory cytokines known to be implicated in the pathogenesis of non-alcoholic fatty liver disease, such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and TNF-α.

On the other hand, the administration of CoQ alone or in combination with Rosi showed a mild improvement in FED-induced histopathological changes in the liver. The current finding is in contrast to those of other investigators who reported the favorable effects of such micronutrients in hepatocellular injury. This contradiction may require further investigation in order to determine the exact responsible mechanism.

The results of the present study also revealed that supplying rats with a FED elevated serum uric acid level. In FED-fed rats, increased plasma uric acid levels have been reported by many authors. Unlike other simple sugars, fructose has the unique ability to increase uric acid production. The first step in the metabolism of fructose is the phosphorylation to fructose-1-P via fructokinase, an enzyme which utilizes adenosine monophosphate (ATP) as a phosphate donor. The accumulation of fructose-1-P depletes hepatic ATP and generates adenosine diphosphate (ADP). Metabolism of ADP stimulates adenosine monophosphate (AMP) deaminase and increases the degradation of nucleotides to form uric acid.

Treatment of insulin-resistant rats with Rosi or CoQ significantly lowered serum uric acid level. Amelioration of insulin resistance by insulin sensitzers was shown to decrease serum uric acid level. The favorable effects of CoQ could be due to its antioxidant properties thus, inhibiting lipid peroxidation by preventing the production of lipid peroxyl radicals. In addition, CoQ administration resulted in the reduction of hyperinsulinemia and insulin resistance consequently, uric acid excretion is increased and lower levels are observed in the serum. A typical consequence for the complementary effect of both Rosi and CoQ was also observed in the current study as the combined agents succeeded in normalizing the elevated serum uric acid level.

Furthermore, the findings of the present study demonstrated that MS in rats was associated with an elevation in serum urea and creatinine levels which reflects impairment in glomerular filtration rate. This was further supported by histological examination of kidney tissues which revealed hemorrhage, congestion and inflammatory cell infiltration of the glomerular tuft. Treatment of insulin-resistant rats with Rosi or its combination with CoQ failed to provoke any significant change in the elevated levels of serum urea and creatinine; however they partly improved hemorrhage and inflammatory cell infiltration of the glomerular tuft although congestion in the tuft was still observed, a fact that may explain the observed ineffectiveness of Rosi or its combination with CoQ on the serum levels of urea and creatinine.

Low-grade inflammation is now recognized as a common feature of the metabolic abnormalities observed in obesity. TNF-α is increased in obesity and has been extensively characterized for its role in insulin resistance. Fructose feeding in rats has been shown to increase hydrogen peroxide generation and inflammatory markers. Increased plasma concentrations of TNF-α have been observed following fructose feeding in mice. Furthermore, TNF-α mRNA increased in hepatic tissues of fructose-fed mice. These findings are in harmony with the results of the present study which showed that maintaining rats on an FED for 16 weeks definitely increased serum TNF-α level.

The results of the present study demonstrated that treating MS rats with Rosi, CoQ or their combination markedly decreased serum TNF-α level. These findings are quite consistent with those of Lee et al. who showed that treating Otsuka Long-Evans Tokushima fatty rats with Rosi reduced serum inflammatory cytokines including TNF-α. Regarding the effect of CoQ, limited data are available in the literature. However, Bessler et al. found that incubation of human peripheral blood mononuclear cells with CoQ markedly reduced TNF-α secretion.

Furthermore, the results of the present study revealed that maintaining rats on an FED for 16 weeks reduced the activities of the antioxidant enzymes; catalase and GSH-Px. Delbosc et al. found that fructose feeding increases oxidative stress.
and is associated with MS in rodents. Enhanced lipid peroxidation in fructose-fed rats could be associated with high circulating glucose levels, which enhance free radical production from glucose autoxidation and protein glycation. Prolonged exposure of rats to hyperglycemic conditions reduces the activities of superoxide dismutase and other antioxidant enzymes.

Treating insulin resistant rats with Rosi slightly raised the reduced plasma catalase and GSH-Px activities. Yilmaz et al. reported the antioxidant properties of the drug and found that Rosi treatment reduced malondialdehyde (MDA) level, a valuable indicator of lipid peroxidation in subjects with MS. The antioxidant effect of Rosi is not mediated by PPAR-γ but strictly depends on its ability to activate AMP-activated protein kinase which in turn, prevents the activity of NADPH-oxidase, a major source for the production of ROS after exposure to hyperglycemia. In addition, Sener et al. reported that treatment with Rosi decreased MDA contents of the liver in rats by inhibiting neutrophil infiltration and the subsequent activation of inflammatory mediators that induce lipid peroxidation. This finding was supported in the present study by the fact that Rosi treatment reversed FED-induced histopathological changes in the livers of insulin resistant rats.

Likewise, CoQ treatment was associated with a mild elevation in the activities of catalase and GSH-Px enzymes. Antioxidant potential of CoQ is related to its capacity to exist in a completely oxidized form and a completely reduced form thus, enabling it to perform its functions in the electron transport chain. CoQ inhibits lipid peroxidation by preventing the production of lipid peroxide radicals. In contrast to other antioxidants, this compound inhibits both the initiation and the propagation of lipid and protein oxidation. It also regenerates other antioxidants such as vitamin E. These data could explain the favorable effects of Rosi and CoQ in this perspective.

5. Conclusions

In conclusion, the findings of the current study prove the benefits of the co-administration of Rosi and CoQ in a fructose-induced model of insulin resistance. Rosi and CoQ, in combination, offer further improvements to markers of disease risk, including lipid profile, hyperglycemia hyperinsulinemia, hyperleptinemia, increased oxidative stress and the level of circulating cytokines.

6. Conflict of interest

None declared.

References

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