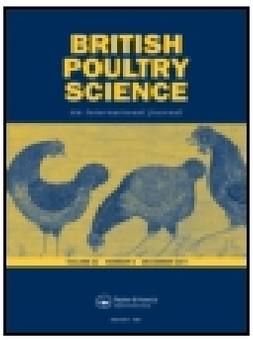

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The effect of dietary coenzyme Q10 on plasma metabolites and hepatic gene expression in broiler breeder hens

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ABSTRACT

1. This study was performed to evaluate the effects of dietary supplementation of coenzyme Q10 (CoQ10) on laying rate, body weight, plasma metabolites and some liver gene expression in broiler breeder hens.
2. A total of 128 broiler breeder hens (Arbor Acres Plus, 47 weeks of age) were randomly distributed to four dietary groups supplemented with different levels of CoQ10 (0, 300, 600 or 900 mg/kg diet) with four replicates of eight hens each. During 47–54 weeks of age, laying rate, egg mass and body weight were recorded weekly. To assay plasma biochemical indicators, blood samples were collected at 54 weeks of age. At the end of the experiment, for evaluating the abdominal fat weight, liver weight and expression of the *adiponectin* and *proliferator-activated receptor-α* (*PPAR-α*) genes in the liver, eight hens per treatment were selected, weighed and humanely killed by decapitation.
3. Dietary supplementation of CoQ10 linearly decreased abdominal fat weight, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities by increased levels of CoQ10. The plasma levels of glucose, cholesterol and alkaline phosphatase (ALP) activity were quadratically decreased by increased levels of CoQ10. The best plasma levels of glucose, cholesterol and ALP activity were estimated at 562.5, 633.3 and 517.8 mg CoQ10/kg diet, respectively. *Adiponectin* and *PPARα* gene expression exhibited a linear increased by increased levels of CoQ10.
4. In conclusion, addition of CoQ10 to the diet influenced lipid metabolism and expression of the *adiponectin* and *PPAR-α* genes, which might be partially due to the improvement in mitochondrial metabolism and energy production. However, further studies are necessary to determine the effects of CoQ10 on these indicators in broiler breeder hens during ageing.

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Adiponectin; body weight; coenzyme Q10; hen; metabolites

Introduction

The diets of broiler chickens usually contain low levels of supplemented fat (often <6% of total calories). Therefore, alterations in tissue and lipoprotein lipid composition are primarily through changes in endogenous fatty acid synthesis and metabolism (Walzem and Chen 2014). The liver produces above 80% of adipose tissues fatty acids, which is in response to feeding/fasting-induced manipulation of insulin signalling (Walzem and Chen 2014). However, it is well determined that insulin resistance exists in the central nervous system (CNS) from broiler breeder chickens, due to persistent hyperinsulinemia, which results in a down-regulation of CNS insulin receptor expression compared to that in layer breeder chickens (Shiraishi et al. 2011). This may result in impairment of feed intake control in broiler chickens and overfeeding during the reproductive development, which, in turn, has adverse effects on reproductive performance and body weight (Cassy et al. 2004; Shiraishi et al. 2011). It has been stated that hyperinsulinism and overfeeding in broiler chickens induce excessive lipid deposition in non-adipose tissue body organs and elevation of blood lipids (Stout et al. 1973). Hence, to increase the reproductive lifespan and control obesity, restricted feeding is used conventionally by breeder producers (Sharideh et al. 2016). However, in studies performed on meat-type fowls during ageing (during 32–54 weeks of age), it has been proven that mitochondrial dysfunction in energy production and increased oxidative stress are associated with decreased reproductive performance (Breque et al. 2006; Iaffaldano et al. 2018). It has been suggested that targeting mitochondria with specific nutrients from natural sources like coenzyme Q10 (CoQ10) can efficiently inhibit various conditions associated with metabolic disturbances and mitochondrial dysfunction (Lapointe 2014).

Coenzyme Q10, a lipid-soluble vitamin-like potent antioxidant, acts as an electron-shuttling compound in the mitochondrial electron transport chain and oxidation-reduction process in all cell membranes (Abadi et al. 2013; Farhangi et al. 2014). Some studies performed with chickens proved that dietary CoQ10 supplementation reduced serum lipid content and ascites mortality, and increased serum antioxidant activity (Geng et al. 2004; Gopi et al. 2015). Reduced CoQ10 can regenerate α-tocopherol from the tocopheroxyl radicals in the mitochondria, and therefore plays an important role in modulating oxidant production (Shetty et al. 2014). It has been shown that exogenous CoQ10 restored mitochondrial oxygen usage to the levels equal to those seen in young mice (Takahashi and Takahashi 2013). Coenzyme Q10 increases gene expression of *adiponectin* and *peroxisome proliferator-activated receptor-α* (*PPAR-α*) genes in mice (Carmona et al. 2009). Adiponectin and PPAR-α have principal positive roles in the regulation of body weight, lipid metabolisms and glucose (Carmona et al. 2009). It has been shown that CoQ10 supplementation in the diet of laying hens decreased total cholesterol levels in plasma (Honda et al. 2013). Blood cholesterol levels increased with age in

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broiler-type hens (28 weeks of age compared to 45 weeks of age) and had a negative effect on reproductive performance (Dikmen and Sahan 2007).

The metabolic status of birds is affected by ageing and strain (broilers compared to layers) and can be enhanced with specific nutrients from natural sources (Faure et al. 2017; Iaffaldano et al. 2018). It seems that CoQ10, as an anti-adipogenic factor, may affect body weight, levels of plasma metabolites, and some liver gene expression in broiler-type hens. The present study was conducted to investigate the effect of dietary CoQ10 on body weight, plasma metabolites and gene expression of *adiponectin* and *PPAR-α genes* in the liver of broiler breeder hens.

Materials and methods

Approval for the current study was given by the Animal Welfare Committee of the Department of Animal Science, University of Tehran.

Birds and treatments

A total of 128 Arbor Acres Plus broiler breeder hens (body weight, 3950.52 ± 293.57 g) were selected at 44 weeks of age from a commercial flock. The hens were randomly distributed to 32- floor pens (1.25 m × 2.5 m; eight hens/pen) provided with a pan feeder and an automatic bell drinker and raised at an ambient temperature of 22 ± 2°C under a 14L:10D photoperiod. The birds were fed a basal diet (Table 1) without CoQ10 (Hangzhou Dingyan Chem Co., Ltd, Hangzhou, China) supplementation for 2 weeks (45 and 46 weeks of age). Afterwards, eight hens were randomly distributed into four replicate pens (n = 4) within each of four dietary treatments. For 8 consecutive weeks, the dietary treatments included either 0 (control group), 300, 600 or 900 mg of CoQ10 per kg of diet. During the experiment (44–54 weeks of age), the breeder hen feed intakes were restricted (according to Arbor Acres Parent Stock Catalog) to a mean of 155 g/day/bird and water was supplied *ad libitum*.

From 47 to 54 weeks of age, the laying rate and egg mass (laying rate × egg weight/100) were calculated weekly. The body weight of the hens was measured weekly to determine body weight gain.

Table 1. Ingredients and chemical composition of the diets fed to breeder hens (as fed basis).

Ingredient	Amount (g/kg)
Corn	664.0
Soybean meal, 42.6% CP	195.0
Wheat bran	34.0
Corn oil	10.0
Dicalcium phosphate	13.0
Mineral oyster shall	73.2
Common salt	3.2
$NaHCO_3$	1.0
Mineral premixes[a]	2.5
Vitamin premix[b]	2.5
DL-Met, 99%	1.6
Calculated nutrient content	
ME (kcal/kg)	2800
CP (%)	14
Calcium (%)	3.2
Available phosphorus (%)	0.33
Sodium (%)	0.18
Methionine (%)	0.39
Methionine + Cysteine (%)	0.65
Lysine (%)	0.74
Threonine (%)	0.56

[a]Provides (per kg of diet): copper (CuSO4 · 5H2O), 10 mg; iodine (KI), 2 mg; iron (FeSO4 · 7H2O), 50 mg; manganese (MnSO4·H2O), 120 mg; selenium (Na2SeO3), 0.3 mg, Zn (ZnO), 110 mg.

[b]Provides (per kg of diet): retinyl acetate (vitamin A), 3.6 mg; cholecalciferol (vitamin D_3), 0.087 mg; DL-*α*-tocopheryl acetate (vitamin E), 90 mg; menadione (vitamin K_3), 5.0 mg; thiamin (vitamin B_1), 3.0 mg; riboflavin (vitamin B_2), 12 mg; D-pantothenic acid (vitamin B5), 13 mg; niacin (vitamin B_3), 50 mg; pyridoxine (vitamin B_6), 6 mg; biotin (vitamin B_7), 0.66 mg; folic acid (vitamin B_c), 2 mg; cobalamin (vitamin B12), 0.03 mg.

Plasma metabolites and enzymatic activities

At 54 weeks of age, two hens were randomly selected from each pen (eight hens per treatment) and 3 ml of blood was collected into heparinised vacuum tubes by venipuncture to assay plasma levels of glucose, lipids and enzymes activity. The blood samples were subjected to centrifugation at 1500 × g for 15 min (18°C) and plasma was collected and stored at −20°C for later analysis. All samples were assayed at the same time to evade inter-assay variation. Plasma levels of glucose, triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL-c) were determined by using a commercial colorimetric assay kit (Parsazmun, Tehran, Iran) with an intra-assay coefficient of variation of 3.4%, 2.3%, 2.2% and 1.4%, respectively. Enzymatic activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were measured by using a commercial colorimetric assay kit (Parsazmun, Tehran, Iran) with an intra-assay coefficient of variation of 1.8%, 3.2% and 3.1%, respectively.

Tissue collection and weighting

At 54 weeks of age, eight hens per treatment were weighed and humanely killed by decapitation. The abdominal fat pad and liver were dissected and weighed. Then, immediately, samples of liver were collected and quick-frozen in liquid nitrogen and stored until further analysis for gene expression.

RNA extraction, cDNA synthesis and gene expression (real-time quantitative PCR)

Total RNA was isolated from the liver using YTzol kit (Yekta Tajhiz Azma Co, Tehran, Iran) according to the manufacturer's protocol. Total RNA was utilised for reverse transcription (20 µl final volume) following the manufacturer's instructions (Cinaclon Co, Tehran, Iran) and *cDNA* was stored at −80°C for consequent real-time quantitative PCR. All real-time quantitative PCR primers were synthesised by Cinaclon (Tehran) Co., Ltd. Primer sequences for *adiponectin, PPAR-α* and *glyceraldehyde-3-phosphate dehydrogenase* (*GAPDH*) genes are shown in Table 2.

The PCR amplifications were conducted in a final volume of 15 µl reaction mixture containing 1 µl of *cDNA*, 7.5 µl RealQ plus 2x master mix green (Ampliqon, Denmark), 0.6 µl (10 µmol/l) of each primer and 5.3 µl sterilised water, using the Rotor-Gene Q System (QIAGEN Hilden, Germany). The cycling conditions were as follows: 15 min at 95°C followed by 40 cycles of denaturation at 95°C for 15 s, 60°C for 30 s and 72°C for 30 s for the *adiponectin* gene; 40 cycles of 94°C at 15 s, 58°C at 30 s and 72°C for 30 s for the *PPAR-α* gene and 40 cycles of 95°C for 30 s, 57°C for 30 s and 72°C for 30 s for the *GAPDH* gene, which was used as a housing keeping gene.

Table 2. Gene-specific primers for real-time quantitative reverse transcription PCR.

Gene name	Primer sequence	Product size (bp)	Annealing temperature (°C)	GenBank Accession
Adiponectin	F: TACAACGAGCAGAACCACTACGAC R: CATAGGTGAAGATCACTGCCTTGTC	151	60	NM_206991
PPARα	F: GGATGCTGGTAGCCTATGGA R: GGACGATCTCCACAGCAAAT	181	58	NM_001001464.1
GAPDH	F: TGGTGACAGCCATTCTTCCA R: TCCAACAAAGGGTCCTGCTT	199	58	K01458.1

PPARα: Peroxisome proliferator-activated receptor-α; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase.

At the end of each PCR, a melting curve analysis was performed at a rate of 0.18°C/s for all genes to check the specificity of the products. Relative quantities of mRNA were analysed using the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

All data were tested for normal distribution and normality of variances by Shapiro–Wilk and Levene's test, respectively. The measurements repeated over time were analysed using the Proc Mixed procedure, and other data were analysed using Proc GLM of SAS 9.1. (SAS Institute, 2002, Cary, NC). The results were represented as least squares means ± SEM (four replicates). Linear, quadratic and cubic contrasts were used for the effects of dietary supplementation of CoQ10 on the measured dependent variable. When quadratic responses ($Y = a \pm bX \pm cX^2$; the response of the dependent variable (Y) to the graded levels of CoQ10 (X)) were determined, the optimal CoQ10 level was calculated by taking the first derivative of the quadratic equation.

Results

During 47–54 weeks of age, the dietary CoQ10 had no effect on egg production and egg mass ($P > 0.05$; data not shown). The effects of dietary CoQ10 on body weight, weekly body weight gain and relative weights of abdominal fat and liver are shown in Table 3. There were no significant differences in body weight and weekly body weight gain. Including CoQ10 to the diet linearly decreased abdominal fat relative weight ($P < 0.05$). Dietary CoQ10 had no effect on liver relative weight.

Data associated with plasma levels of triglyceride, cholesterol, HDL-c and glucose are shown in Table 4. The effect of CoQ10 on plasma levels of glucose and cholesterol was significantly reduced compared to the control group. The plasma levels of glucose ($Y = 270.44–0.18X + 0.00016X^2$) and cholesterol ($Y = 161.65–0.19X + 0.00015X^2$) were quadratically decreased by increased levels of CoQ10. The best plasma levels of glucose and cholesterol were estimated to be 562.5 and 633.3 mg CoQ10/kg diet, respectively. The CoQ10 treatment had no significant effect on plasma levels of triglyceride and HDL-c.

The effects of adding CoQ10 to the diet on plasma enzymes activity are shown in Table 5. Including CoQ10 to the diet linearly reduced the activity of AST and ALT. Dietary CoQ10 significantly reduced the activity of the ALP compared to the control group ($P < 0.05$). The ALP activity ($Y = 90.46–0.058X + 0.000056X^2$) was quadratically

Table 3. The effects of different levels of coenzyme Q10 (CoQ10) on body weight (BW), weekly body weight gain (BWG), abdominal fat weight (AFW) and liver weight (LW) in broiler breeder hens for eight successive weeks.

CoQ10 levels (mg/kg diet)	BW at 47 weeks of age (g)	BW at 54 weeks of age (g)	BWG (g)	AFW (% BW)	LW (% BW)
0	3986.53	4088.59	12.75	2.41	1.75
300	4049.03	4120.40	8.82	2.23	1.73
600	3952.00	4017.18	8.14	2.08	1.89
900	4000.87	4073.75	9.09	1.76	1.86
SEM	49.29	45.46	3.57	0.21	0.09
P-value[a]					
Con vs CoQ10	>0.10	>0.10	>0.10	>0.10	>0.10
Linear	>0.10	>0.10	>0.10	<0.05	>0.10
Quadratic	>0.10	>0.10	>0.10	>0.10	>0.10
Cubic	>0.10	>0.10	>0.10	>0.10	>0.10

Values are least squares means ± SEM (number of replicate = 4).
SEM: Standard error of the mean.
[a]*P* values include the linear, quadratic and cubic responses, and orthogonal contrast between CoQ10 levels (300, 600 or 900 mg CoQ10/kg diet) with the control group (Con; the hens fed basal diet without CoQ10).

Table 4. Plasma levles of glucose, triglycerides, total cholesterol and high-density lipoprotein cholesterol (HDL-c) in broiler breeder hens fed the diet supplemented with different values of coenzyme Q10 (CoQ10) for 8 successive weeks.

CoQ10 level	Glucose (mg/dl)	Triglycerides (mg/dl)	Cholesterol (mg/dl)	HDL-c (mg/dl)
0	272.11	1496.18	163.58	81.06
300	225.36	1338.96	110.55	71.96
600	224.86	1375.26	105.35	81.23
900	237.32	1332.47	109.18	82.95
SEM	8.70	130.63	13.86	5.15
P-value[a]				
Con *vs.* CoQ10	<0.01	>0.10	<0.01	>0.10
Linear	<0.05	>0.10	<0.05	>0.10
Quadratic	<0.01	>0.10	<0.05	>0.10
Cubic	>0.10	>0.10	>0.10	>0.10

Values are least squares means ± SEM (number of replicate = 4).
SEM: Standard error of the mean.
[a]*P* values include the linear, quadratic and cubic responses, and orthogonal contrast between CoQ10 levels (300, 600 and 900 mg CoQ10/kg diet) with the control group (Con; the hens fed basal diet without CoQ10).

Table 5. Plasma enzymatic activities of alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) concentrations in broiler breeder hens fed the diet supplemented with different values of coenzyme Q10 (CoQ10) for 8 successive weeks.

CoQ10 levels (mg/kg diet)	ALP (U/l)	ALAT (U/l)	ASAT (U/l)
0	91.45	13.60	47.28
300	75.10	12.41	35.70
600	78.39	11.43	29.63
900	82.77	10.30	31.98
SEM	4.82	1.13	3.77
P-value[a]			
Con vs CoQ10	<0.05	>0.10	<0.01
Linear	>0.10	<0.05	<0.01
Quadratic	<0.05	>0.10	<0.10
Cubic	>0.10	>0.10	>0.10

Values are least squares means ± SEM (number of replicate = 4).
SEM: Standard error of the mean.
[a]*P* values include the linear, quadratic and cubic responses, and orthogonal contrast between CoQ10 levels (300, 600 and 900 mg CoQ10/kg diet) with the control group (Con; the hens fed basal diet without CoQ10).

Table 6. Relative mRNA expression of *adiponectin* and *peroxisome proliferator-activated receptor-α* (*PPAR-α*) in hen livers fed the diet supplemented with different values of coenzyme Q10 (CoQ10) for 8 successive weeks.

CoQ10 level	*Adiponectin*	*PPAR-α*
0	1.18	0.51
300	1.44	0.79
600	1.39	0.68
900	1.96	1.16
SEM	0.18	0.14
P-value[a]		
Con vs CoQ10	<0.10	<0.05
Linear	<0.05	<0.01
Quadratic	>0.10	>0.10
Cubic	>0.10	>0.10

Values are least squares means ± SEM (number of replicate = 4).
SEM: Standard error of the mean.
[a]*P* values include the linear, quadratic and cubic responses, and orthogonal contrast between CoQ10 levels (300, 600 and 900 mg CoQ10/kg diet) with the control group (Con; the hens fed basal diet without CoQ10).

decreased in treated groups. The lowest level of ALP activity was estimated at 517.8 mg CoQ10/kg diet.

The effect of adding CoQ10 to the diet on gene expression of *adiponectin* and *PPAR-α* in the liver is shown in Table 6. *Adiponectin* and *PPAR-α* gene expression exhibited a linear increase with rising levels of CoQ10 supplementation. The highest level of gene expression of *adiponectin* and *PPAR-α* was observed in hens receiving 900 mg CoQ10/kg diet.

Discussion

In the present study, although the addition of CoQ10 to the diet showed a trend for decreased body weight and weight gain in hens, but decreased relative abdominal fat weight and plasma levels of cholesterol. A study performed on *ob/ob* mice showed that CoQ10 supplementation prevented body weight gain and increased lipid oxidation in adipose tissue (Carmona et al. 2009). Also, it has been shown that antioxidant activity decreased during ageing in broiler breeder hens (Breque et al. 2006) and adding antioxidants, such as α-tocopherol in the diet, changed antioxidant levels and decreases liver lipid (Zaghari et al. 2013). Similar to the current results, studies in mice and broiler chickens showed that supplementary CoQ10 reduced serum lipid content, abdominal fat in broilers and total fat mass in mice (Carmona et al. 2009; Gopi et al. 2014, 2015). Therefore, it appears that dietary supplementation with CoQ10 can alter lipid oxidation in adipose tissues, such as abdominal fat, which in turn, decreased fat storage.

Blood activity of liver enzymes, used as indexes of hepatic health, can be increased during certain metabolic disorders, such as insulin resistance and obesity (Amin et al. 2014). It has been reported that elevation of activity of liver enzymes has been associated with a raised blood level of glucose (Noordam et al. 2017). In the present study, addition of CoQ10 to the diet decreased the activity of ALT, AST and ALP and reduced plasma glucose and cholesterol. The results indicated that dietary CoQ10 supplementation can alter liver activity and lipid metabolism. Studies performed on rats have proven that supplementation of the diet with CoQ10 decreased serum AST and ALT activity during metabolic stress (Ashkani-Esfahani et al. 2016; Farhangi et al. 2014; Vasiliev et al. 2011). Farhangi et al. (2014) showed that CoQ10 supplementation in patients with non-alcoholic fatty liver disease decreased waist circumference and serum AST. Elevation of liver enzymes, such as aminotransferases, is related to hepatic gluconeogenesis and/or inflammation in insulin resistance patients (Amin et al. 2014). Therefore, decreasing activity of liver enzymes by adding CoQ10 to the hens' diet may explain the decreased gluconeogenesis in the hepatic cell (as indicated decreased blood levels of glucose).

According to the published data, this is the first paper to show that dietary supplementation of CoQ10 linearly increased gene expression of *PPAR-α* and *adiponectin* in the hepatic cells of the hens. Previous studies in mammals have been shown that decreased ROS production by CoQ10 can improve mitochondrial function and regulation of some genes sensitive to ROS, such as *PPAR-α* and *adiponectin* (Carmona et al. 2009; Gholami et al. 2018). Therefore, using a potent antioxidant such as CoQ10 may improve metabolic disturbances during oxidative stress conditions. Peroxisome proliferator-activated receptor-α and adiponectin have been identified as key players in the alteration of lipid and cholesterol metabolism (Schmelzer et al. 2011). Studies in humans and mice showed increased gene expression of *PPAR-α* by supplementation with CoQ10 resulted in reduced blood cholesterol (Schmelzer et al. 2011, 2010). Birds exposed to food deprivation showed decreased expression of the *adiponectin* gene (Maddineni et al. 2005). This indicated that the resulting adiponectin has a key role in regulating gluconeogenesis and insulin sensitivity. It has been reported that adiponectin stimulates glucose utilisation and suppress gluconeogenic enzymes and gluconeogenic substrate availability and acts as a shield against lipotoxicity (Combs and Marliss 2014; Ramachandran et al. 2007). Adiponectin has a significant impact on the impairment of adipocyte differentiation, as well as decreased fat deposition in chickens (Yan et al. 2014). Studies in rats and humans, as well as this study, showed that including CoQ10 to their diet improved insulin sensitivity, the serum lipid profile and adiponectin, and decreased serum levels of AST and ALT (Amin et al. 2014; Gholami et al. 2018). Therefore, it appeared that adding CoQ10 to the diet of broiler breeder hen improved *adiponectin* and *PPAR-α* gene expression and suppressed the gluconeogenesis pathway, which decreased plasma levels of glucose, cholesterol and abdominal fat.

Conclusions

Supplementation of CoQ10 in the diet influenced lipid metabolism and expression of the *adiponectin* and *PPAR-α* genes, which may be partially associated with an improvement in mitochondrial metabolism and energy production. However, further studies are necessary to determine the effects of CoQ10 on such indicators in broiler breeder hens during ageing.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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