

24-HOUR FOLLOW-UP STUDY OF PLASMA COENZYME Q₁₀, TOTAL ANTIOXIDANT CAPACITY AND SELECTED BLOOD PARAMETERS AFTER A SINGLE ORAL DOSE OF WATER-SOLUBLE COENZYME Q₁₀ IN HEALTHY BEAGLE DOGS

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Summary: Coenzyme Q (CoQ₁₀) is one of the most promising compounds in antioxidant therapy, due to its key role in mitochondria and its antioxidant action. It has been shown to have positive effects in the treatment of many diseases in humans. In contrast, there are only a limited number of studies and experimental data on CoQ₁₀ supplementation in dogs. In the present study, changes of plasma CoQ₁₀, serum total antioxidant capacity (TAC), and selected haematological and biochemical parameters were followed over 24 hours in healthy beagle dogs, following the administration of a single oral dose of 30 mg of water-soluble CoQ₁₀. Correlations between plasma CoQ₁₀ and serum TAC, and between TAC and albumin, a potent plasma antioxidant, were also investigated. A statistically significant increase of plasma CoQ₁₀ was demonstrated as early as 20 minutes after CoQ₁₀ administration, with a peak value four hours after administration. Contrary to expectation, simultaneous increases of plasma CoQ₁₀ and TAC were not observed, however, a positive, statistically significant correlation between the latter two parameters was observed one hour after the administration of CoQ₁₀ ($p = 0.011$), indicating a contribution of CoQ₁₀ to the TAC of canine serum. The correlation, now close to statistical significance ($p = 0.052$), remained when plasma CoQ₁₀ reached its peak value. The positive, statistically significant correlations between albumin and serum TAC, determined at basal measurements and 40 minutes and 1, 4 and 6 hours later, indicate a significant contribution of albumin to the TAC of canine serum. Selected haematological and biochemical parameters over 24 hours showed the diurnal variations normally found in dogs. Further investigation is needed to establish the influence of long-term CoQ₁₀ supplementation on TAC in dogs.

Key words: coenzyme Q₁₀; total antioxidant capacity; dogs

Introduction

Coenzyme Q (CoQ) or ubiquinone is an endogenous compound located widely in living organisms. It is a lipid, composed of a redox active benzoquinone ring and a hydrophobic side chain comprising from 6 (CoQ₆) to 10 (CoQ₁₀) isoprenoid units, depending on species (1, 2). In humans and most mammals, including dogs, the predominant form is CoQ₁₀, which is the same as that available as an oral formulation

(1, 3). CoQ₁₀ is present in two redox forms, namely ubiquinone-10 (CoQ₁₀, oxidized form) and ubiquinol-10 (CoQ₁₀H₂, reduced form). The latter is the predominant form in blood and most other tissues, where it behaves as a phenolic antioxidant (1, 4, 5, 6, 7, 8).

CoQ has several biochemical functions. As an intermediate of the electron transport system in mitochondria it plays a key role in cellular respiration and production of adenosine triphosphate (ATP). The reduced form of CoQ, ubiquinol, is the only known lipid-soluble antioxidant synthesized *de novo* in human and all animal tissues, and mechanisms exist that can generate it from ubiquinone as

a result of its antioxidant activity. Its strong hydrophobicity allows the insertion of the molecule into the membrane phospholipid bilayer in proximity to the unsaturated lipid chains, where it acts as a primary scavenger of free radicals and thus prevents lipid peroxidation in most subcellular membranes. The protective effect of ubiquinol includes not only lipids, but extends to proteins and DNA (1, 2, 5, 9, 10-14). In addition to its direct antioxidant function, ubiquinol regenerates α -tocopherol by reducing the α -tocopheryl radicals produced by reaction with lipid or oxygen (1, 11, 15), and is responsible for the extracellular stabilization of ascorbate with its NADH-dependent reductase (16).

There is also evidence for a function of CoQ in redox control of cell signalling and gene expression, from studies on coenzyme Q stimulation of cell growth, inhibition of apoptosis, control of thiol groups, formation of hydrogen peroxide and control of membrane channels (11, 12, 17, 13).

CoQ₁₀ is emerging as prophylactic and therapeutic agent. It is one of the most promising compounds in antioxidant therapy, due to its key role in mitochondria and antioxidant action (1, 4, 5, 10, 11, 13, 18). In human studies CoQ₁₀ has been shown to be a valuable component in treating cardiovascular (1, 4, 19, 20), neurodegenerative (1, 9, 21, 22) and renal diseases (23, 24), as well as male infertility (4, 9, 25) and cancer (9, 26). It is also able to inhibit oxidative damage, to enhance DNA repair enzyme activity in human cultured lymphocytes (27) and to prevent many of the detrimental effects of photoaging on the skin (28).

Although there are some basic similarities in the function of CoQ₁₀ in humans and other animals, only a limited number of studies and experimental data about CoQ₁₀ supplementation have been reported on dogs. So far, CoQ₁₀ has been used as a supportive therapy for cardiac and hepatic diseases, in mitochondrial diseases and as a neuroprotectant in dogs (6, 29, 30, 31).

The aim of this 24-hour follow-up study was to determine changes of plasma CoQ₁₀, serum total antioxidant capacity (TAC) and selected blood parameters in healthy beagle dogs, following a single oral dose of water-soluble CoQ₁₀. The study was also aimed to determine whether there is a correlation between plasma CoQ₁₀ and serum TAC. The reduced form of CoQ₁₀, the predominant form in plasma and tissues, exerts antioxidant properties and TAC is a biochemical parameter suitable for evaluating the overall antioxidant status of serum or plasma re-

sulting from antioxidant intake and/or production, and their consumption by the normal or increasing levels of oxidative stress (32-36). In addition, correlations between albumin and serum TAC were determined at each sampling time. Albumin is the predominant circulating antioxidant agent, since each albumin molecule contains one single cysteine with a free SH group that participates in redox reactions. Furthermore, albumin, urate and ascorbate make up the major contribution to the TAC of human plasma, largely due to their high concentrations relative to those of other blood antioxidants such as bilirubin, α -tocopherol, β -carotene, glutathione, ubiquinol-10, as well as those not yet recognized (34-38).

Materials and methods

Animals

7 adult beagle dogs, 1 female and 6 male, weighing between 16.5 and 22.6 kg with an average body weight of 19.5 kg, were used in this study. They were considered healthy on the basis of history, results of physical examination and of haematological and serum biochemical analysis. The dogs were housed in couples in cages of appropriate size in a room with room temperature between 18 and 21°C, fed a commercial dry and canned diet (Pedigree Pal, Mars Incorporated, USA) three times a day, with unlimited access to water. They were walked in pairs for at least 20 minutes three times per day. Social contacts between the caretakers and dogs were carried out during the day.

All procedures complied with the relevant Slovenian governmental regulations (Animal Protection Act UL RS, 43/2007) and were approved by Ministry of Agriculture, Forestry and Food, Veterinary Administration of the Republic of Slovenia; license No 323-02-818/2005.

Study protocol and collection of blood samples

Each dog received a single dose of water soluble paste containing 7.5 % of CoQ₁₀ in the form of an inclusion complex with β -cyclodextrin, that was synthesized in the Laboratory for Food Chemistry, National Institute of Chemistry (Ljubljana, Slovenia) according to previously filed patents (39, 40). 400 mg of paste, equivalent to 30 mg of CoQ₁₀, was added into the food and given with the morning meal (Pedigree Pal, Mars Incorporated, USA) at 8 a.m. Ve-

nous blood samples for determination of CoQ₁₀, total antioxidant capacity (TAC), and haematological and biochemical parameters were collected before (basal values), and 20 and 40 minutes, 1, 2, 4, 6, 10 and 24 hours after dosing. The dogs were fed three times a day, at 8 a.m., 2 p.m. (6 h after dosing) and at 6 p.m. (10 h after dosing), each time after blood was collected. Water was available *ad libitum*.

Blood samples for CoQ₁₀ were collected in heparinized Vacutainer® tubes (Vacutainer Systems, Becton Dickinson, Franklin Lakes, New Jersey, USA) and immediately centrifuged at 1500 g for 15 minutes at 4°C. Plasma was separated and immediately frozen at -80°C until analysis. Blood samples were collected into serum separator tubes (Vacuette, Greiner Bio-One, Kremsmunster, Austria) and into EDTA-containing tubes (Mictrotainer™, Beckton and Dickinson, Franklin Lakes, USA). Samples in serum separator tubes were stood for 30 min at 4°C to clot, then centrifuged (1300 g for 10 min) to separate the serum. Serum samples were stored at -80°C and assayed in duplicate within 2 weeks for TAC and various biochemical parameters including glucose (Glu), urea, creatinine (Crea), sodium (Na), potassium (K), chloride (Cl), calcium (Ca), inorganic phosphate (iP), total protein (TP), albumin (Alb), alanine aminotransferase (ALT) and alkaline phosphatase (AP). EDTA blood samples for complete blood count (CBC) and white cell differential count (WCDC) determinations were stored at room temperature and analysed between 1 and 5 h after sampling.

Plasma CoQ₁₀ determination

Plasma CoQ₁₀ was determined at the National Institute of Chemistry (Ljubljana, Slovenia) by HPLC/MS as previously described in a bioavailability study of water-soluble CoQ₁₀ in dogs (41). Plasma samples (400 µL) were denatured with 200 µL of 10% perchloric acid in ethanol (v/v) and extracted three times with 2 mL of n-hexane. The combined organic extracts were concentrated with a rotary evaporator (Rotavapor R-144 equipped with a water bath B-480, Büchi, Flawil, Switzerland). The residue was redissolved in 200 µL of 2-propanol and analyzed by HPLC/MS.

Determination of TAC

Serum samples from 7 healthy beagle dogs were assayed for TAC using an automated chemistry analyser (RA-XT, Siemens/Bayer (former Technicon),

Munich, Germany), using a commercially available Total Antioxidant Status (TAS) kit (Randox, Crumlin, UK), following the manufacturer's instructions. The assay (32) is based on the reduction of free radicals (ABTS^{•+}-2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonate)) by antioxidants, measured as a decrease of absorbance at 600 nm at 3 min. The ABTS^{•+} radical cation is formed by the interaction of ABTS with the ferrylmyoglobin radical generated by the activation of metmyoglobin with hydrogen peroxide. The suppression of the absorbance of the ABTS^{•+} radical cation by serum antioxidants was compared with that by Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid), which is included as part of the TAS kit. The results are expressed as mmol/l of Trolox equivalents.

Determination of biochemical parameters

Glucose, urea, creatinine, calcium, inorganic phosphate, total protein, albumin, AP and ALT were determined by automated chemistry analyser (RA-XT, Siemens/Bayer (former Technicon), Munich, Germany). Electrolytes, Na, K and Cl, were determined by electrolyte analyser Ilyte Na/K/Cl (Instrumentation Laboratory, Lexington, MA, USA).

Determination of haematological parameters

CBC and WCDC were determined by an automated laser haematology analyser H*1 (Siemens/Bayer (former Technicon), Munich, Germany) with species specific software (H*1 Multi-Species V30 Software, Tarrytown, New York, USA). The resulting CBC includes white blood cells (WBC), red blood cells (RBC), haemoglobin concentration (HGB), haematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) and platelets (PLT). WCDC comprises six-part differential: neutrophils (NEUT), lymphocytes (LYMPH), monocytes (MONO), eosinophils (EOS), basophils (BASO) and large unstained cells (LUC), all as percentages. The LUC category consists of a heterogeneous population of all large cells that fail to exhibit any peroxidase activity (atypical lymphocytes, immature granulocytes and blasts).

Statistical evaluation

Data were analysed with commercial software (SPSS 15.0, Chicago, Illinois, USA). For each param-

eter measured the data were examined for normality using the Kolmogorov and Smirnov test (42). Means and standard deviations (SD) were calculated for plasma CoQ₁₀, serum TAC and selected biochemical and haematological parameters. Repeated measures ANOVA was used to test for statistically significant differences of parameters between basal samples and 8 consecutive samples within the 24-hour measuring period. Pearson's correlation coefficient analysis was performed to determine whether there were statistically significant correlations between plasma CoQ₁₀ and serum TAC and between albumin and serum TAC at different sampling times. A value of $p < 0.05$ was considered significant.

Results

Administration of a single oral dose of water-soluble CoQ₁₀ to healthy beagle dogs resulted in a significant increase in plasma CoQ₁₀ (Table 1) as early as 20 min after basal measurements, and remained significantly increased during the rest of the measuring period. Plasma CoQ₁₀ reached a peak value of 1.21 ± 0.48 mg/L, four hours after the basal sampling that gave a mean endogenous plasma CoQ₁₀ value of 0.36 ± 0.09 mg/L. After reaching the peak concentration, CoQ₁₀ decreased continuously from the 6th to the 24th hour after administration to a final value of 0.70 ± 0.17 mg/L.

Serum TAC (Table 1) decreased significantly 2 hours after basal sampling, from 0.948 ± 0.240 to 0.674 ± 0.132 mmol/L. It then increased from the 4th to the 24th hour after CoQ₁₀ administration to a final value of 0.986 ± 0.152 mmol/L.

Albumin concentration (Table 1) remained within the normal reference range (43,44) at all sampling times without significant changes from basal values.

A positive, statistically significant correlation (Table 1) was found between plasma CoQ₁₀ and serum TAC one hour after basal sampling ($r = 0.869$; $p = 0.011$). Four hours after basal measurements, when plasma CoQ₁₀ had reached its peak value, a positive correlation close to statistical significance ($r = 0.808$; $p = 0.052$) was determined. Though not significant, nearly all correlations at other sampling times were positive, with the exception of a negative correlation found at 10 hours after the administration of CoQ₁₀.

A positive, significant correlation between albumin and serum TAC (Table 1) was determined at basal sampling and 40 minutes, 1, 4 and 6 hours later.

Correlations at the remaining time points were also positive.

All serum biochemical parameters, with the exception of AP and albumin, showed statistically significant changes from basal values at all sampling times of the 24-hour measuring period (Table 2). Basal measurements showed that, with the exception of AP and inorganic phosphate, all other biochemical parameters were within the normal reference range (43, 44). At other sampling times however, biochemical parameters showed minor deviations from the normal reference range.

Haematological parameters, with the exception of LUC, differed statistically significantly from basal values throughout the 24-hour measuring period (Table 3). All basal haematological values were within the normal reference range (43, 45). On the other hand there were minor deviations of MCH, MCHC, NEUT and LYMPH from normal values at other sampling times of the 24-hours measuring period.

Discussion

A limited number of studies and experimental data about CoQ₁₀ supplementation in different physiological and pathological conditions in dogs are available in the literature (30, 31, 41, 46, 47). In contrast, there is a great interest and progress in this area of human medicine, where numerous studies have confirmed that CoQ₁₀, due to its key role in mitochondria and antioxidant action (1, 5, 9, 10, 11, 13), is one of the most promising compounds in antioxidant therapy of cardiovascular (1,4, 19, 20), neurodegenerative (1, 9, 21, 22), renal (23, 24) and immune diseases (27), as well as in male infertility (4,9, 25), cancer (9, 26) and several other disorders.

In the present study, changes of plasma CoQ₁₀, serum TAC and selected haematological and biochemical parameters were followed over 24 hours in healthy beagle dogs after administration of a single oral dose of water-soluble CoQ₁₀. The reduced form of CoQ₁₀, ubiquinol-10, is an antioxidant and also a predominant form of CoQ₁₀ in human and canine plasma and tissues (1, 4, 5, 6, 7, 8), therefore, in our study we aimed to determine whether there is a correlation between plasma CoQ₁₀ and serum TAC at different sampling times. Correlations between albumin and serum TAC were also determined, since the antioxidant properties of albumin and its contribution to the TAC of human plasma are well known (32, 34-38).

Table 1: Plasma CoQ₁₀, serum TAC and albumin concentration (mean ± SD) and correlations between plasma CoQ₁₀ and serum TAC and between albumin and serum TAC at different sampling times within a 24-hour measuring period

Parameter/Time of sampling	Basal value	20 min	40 min	1 h	2 h	4 h	6 h	10 h	24 h
CoQ ₁₀ (mg/L)	0.36 ± 0.09	0.45 ± 0.10*	0.51 ± 0.07*	0.61 ± 0.10*	1.00 ± 0.37*	1.21 ± 0.48*	0.88 ± 0.27*	0.77 ± 0.18*	0.70 ± 0.17*
TAC (mmol/L)	0.948 ± 0.240	0.814 ± 0.252	0.844 ± 0.114	0.820 ± 0.131	0.674 ± 0.132*	0.804 ± 0.124	0.868 ± 0.090	0.862 ± 0.073	0.986 ± 0.152
Pearson correlation coefficient (r) ^a	0.451	0.044	0.540	0.869	0.164	0.808	0.477	-0.068	0.473
p value ^a	0.309	0.926	0.211	0.011 \square	0.793	0.052	0.279	0.898	0.510
Alb (g/L)	34.5 ± 3.8	35.1 ± 4.1	34.0 ± 4.1	34.7 ± 3.9	35.4 ± 4.2	34.4 ± 3.6	34.8 ± 3.8	35.1 ± 3.9	34.7 ± 3.9
Pearson correlation coefficient (r) ^b	0.792	0.547	0.935	0.815	0.678	0.972	0.837	0.206	0.466
p value ^b	0.034 \square	0.204	0.002 \square	0.025 \square	0.138	0.001 \square	0.019 \square	0.696	0.292

* p < 0.05 in comparison with basal values

^acorrelations between plasma CoQ₁₀ and serum TAC \square statistically significant correlation^bcorrelations between albumin and serum TAC**Table 2:** Selected biochemical parameters (mean ± SD) at different sampling times within a 24-hour measuring period

Parameter/Time of sampling	Basal value	20 min	40 min	1 h	2 h	4 h	6 h	10 h	24 h
Glu (mmol/L)	5.10 ± 0.36	5.72 ± 0.29*	5.71 ± 0.14*	5.68 ± 0.33*	5.95 ± 0.32*	5.70 ± 0.17*	5.47 ± 0.18*	6.00 ± 1.07	5.22 ± 0.16
Urea (mmol/L)	6.54 ± 1.74	6.11 ± 1.77	6.17 ± 1.83	6.57 ± 1.82*	6.75 ± 2.10*	6.29 ± 2.04	5.90 ± 1.87*	6.48 ± 1.49	6.04 ± 1.64
Crea (μmol/L)	71.5 ± 15.7	71.7 ± 16.2	68.0 ± 13.8	60.6 ± 13.2*	78.7 ± 28.0	68.2 ± 22.9	62.7 ± 21.9	55.5 ± 14.8	71.3 ± 15.1
Na (mmol/L)	148.0 ± 1.0	147.8 ± 0.8	147.2 ± 0.7	146.9 ± 0.6*	146.9 ± 0.9*	148.3 ± 0.5	147.0 ± 0.8*	148.4 ± 1.6	148.3 ± 0.9
K (mmol/L)	5.32 ± 0.37	4.92 ± 0.40*	4.74 ± 0.34*	4.79 ± 0.13*	4.99 ± 0.28	4.82 ± 0.20*	5.00 ± 0.31*	5.09 ± 0.44	4.87 ± 0.32*
Cl (mmol/L)	113.5 ± 1.4	113.3 ± 1.8	112.6 ± 1.9	112.7 ± 1.2	111.6 ± 1.6*	110.7 ± 1.9*	110.5 ± 1.5*	112.4 ± 2.5	111.4 ± 2.0*
Ca (mmol/L)	2.40 ± 0.12	2.36 ± 0.13	2.30 ± 0.11	2.54 ± 0.17	2.78 ± 0.43	2.84 ± 0.44*	2.51 ± 0.18	2.91 ± 0.54	2.44 ± 0.11
iP (mmol/L)	1.74 ± 0.21	1.62 ± 0.14*	1.63 ± 0.13	1.95 ± 0.10*	2.32 ± 0.31*	1.98 ± 0.29	1.65 ± 0.14	2.01 ± 0.30	1.59 ± 0.15
AP (U/L)	217.9 ± 173.4	216.1 ± 171.2	214.4 ± 170.2	214.4 ± 172.1	212.2 ± 170.5	229.4 ± 186.3	228.1 ± 183.7	213.4 ± 175.1	221.1 ± 180.6
ALT (U/L)	72.5 ± 34.4	78.1 ± 35.8	74.6 ± 35.0	89.4 ± 36.7*	78.0 ± 33.0	81.5 ± 35.2	78.8 ± 36.1	80.9 ± 32.8	73.8 ± 33.3
TP (g/L)	67.6 ± 3.6	67.7 ± 3.2	66.0 ± 2.8	72.5 ± 3.7*	80.1 ± 8.1*	72.6 ± 7.6	68.2 ± 4.5	75.8 ± 12.7	66.7 ± 3.1

* p < 0.05 in comparison with basal values

Table 3: Haematological parameters (mean ± SD) at different sampling times within a 24-hour measuring period

Parameter/Sampling time	Basal value	20 min	40 min	1 h	2 h	4 h	6 h	10 h	24 h
WBC (x10 ⁹ /L)	10.55 ± 2.66	10.50 ± 2.84	10.74 ± 3.03	10.65 ± 2.87	11.09 ± 3.25	10.38 ± 3.17	10.00 ± 3.00	10.44 ± 2.86	9.47 ± 2.55*
RBC (x10 ¹² /L)	6.114 ± 0.658	5.957 ± 0.681	6.008 ± 0.664	6.002 ± 0.708	5.754 ± 0.724*	5.635 ± 0.594*	5.892 ± 0.713	5.977 ± 0.586	5.862 ± 0.803
HGB (g/L)	147.1 ± 14.9	142.7 ± 15.4*	144.0 ± 14.6	144.7 ± 15.5*	142.2 ± 15.4*	136.7 ± 12.6	140.7 ± 15.5	146.8 ± 12.3	139.7 ± 16.2
HCT (l/L)	0.410 ± 0.039	0.400 ± 0.040	0.404 ± 0.040	0.407 ± 0.041	0.388 ± 0.041*	0.380 ± 0.035*	0.391 ± 0.042	0.435 ± 0.035*	0.388 ± 0.048
MCV (fl)	67.11 ± 1.68	67.14 ± 1.48	67.28 ± 1.57	67.51 ± 1.49	67.56 ± 1.64*	67.50 ± 1.43	66.44 ± 1.71*	73.05 ± 1.71*	66.51 ± 1.37*
MCH (pg)	24.08 ± 0.71	23.98 ± 0.58	23.97 ± 0.69	24.12 ± 0.61	24.78 ± 1.04*	24.24 ± 0.94	23.90 ± 0.59	24.58 ± 0.72*	23.87 ± 0.58
MCHC (g/L)	358.8 ± 5.2	357.5 ± 3.9	356.4 ± 3.4	357.4 ± 4.6	366.7 ± 8.2*	359.2 ± 8.2	359.7 ± 3.3	336.4 ± 5.9*	359.0 ± 2.4
PLT (x10 ⁹ /L)	418.7 ± 79.2	397.7 ± 71.5*	401.4 ± 66.4	403.8 ± 73.4	442.2 ± 77.6*	429.0 ± 63.8	403.0 ± 68.4	403.0 ± 65.2	393.5 ± 56.6
NEUT (%)	64.47 ± 4.90	64.27 ± 4.13	64.17 ± 3.95	64.68 ± 4.31	61.61 ± 4.15*	61.56 ± 5.78	60.70 ± 4.53*	58.52 ± 3.46*	58.38 ± 5.55*
LYMPH (%)	30.27 ± 4.54	30.32 ± 3.83	30.41 ± 3.52	29.88 ± 4.04	32.54 ± 4.29*	32.50 ± 4.87	33.54 ± 4.39*	32.47 ± 2.88	35.75 ± 5.21*
MONO (%)	2.257 ± 0.310	2.400 ± 0.597	2.129 ± 0.499	2.229 ± 0.811	2.600 ± 0.914	2.400 ± 0.391	1.986 ± 0.414	3.414 ± 0.931*	2.071 ± 0.878
EOS (%)	2.657 ± 0.939	2.671 ± 0.834	2.814 ± 0.859	2.757 ± 0.896	2.729 ± 0.763	3.086 ± 1.027	3.414 ± 0.773*	5.171 ± 1.361*	3.429 ± 1.095*
BASO (%)	0.114 ± 0.900	0.129 ± 0.049	0.157 ± 0.054	0.157 ± 0.079	0.157 ± 0.054	0.143 ± 0.054	0.129 ± 0.049	0.186 ± 0.069*	0.143 ± 0.054
LUC (%)	0.200 ± 0.0816	0.229 ± 0.0951	0.371 ± 0.160	0.286 ± 0.122	0.357 ± 0.162	0.300 ± 0.163	0.257 ± 0.113	0.229 ± 0.170	0.214 ± 0.900

* p < 0.05 in comparison with basal values

The administration of CoQ₁₀ resulted in a significant increase in plasma CoQ₁₀ concentration as early as 20 minutes after basal measurements, reaching a peak value of 1.21 ± 0.48 mg/L at four hours, then slowly decreasing until the final measurement at 24 hours, as already reported in a bioavailability study of water soluble CoQ₁₀ (41). These results are in agreement with those of a bioavailability study of oral CoQ₁₀ formulations (46), in which dogs received 60 mg (2 x 30 mg) of CoQ₁₀ in three different formulations. The mean endogenous plasma CoQ₁₀ in dogs prior to oral administration of CoQ₁₀ was in general agreement with our basal values of CoQ₁₀, 0.21 ± 0.07 mg/L and 0.36 ± 0.09 mg/L, respectively. Basal plasma CoQ₁₀ values in the present study were lower than the serum CoQ₁₀ values of the control group of dogs in a study of Harker-Murray et al. (31). The difference is presumably due to different types of sample used and methods of measurements applied.

Normally, CoQ₁₀ is obtained from food intake, with meat being the largest source in the normal diet (48-50), as well as through endogenous synthesis. In blood, it is transported by plasma lipoproteins, primarily LDL (51), and its plasma levels are in fact considered to be an index of metabolic demand of various tissues under different physiological and pathological conditions (52). Supplementation with CoQ₁₀ has been shown to lead primarily to increased plasma levels, which may account for most of the reported beneficial effects of CoQ₁₀ supplementation in various instances and clinical medicine (2, 6, 7). Furthermore, Weber et al. (53) showed that supplementation with CoQ₁₀ not only increased plasma ubiquinol-10 level, but also lowered the plasma level of TBARS (thiobarbituric acid reactive substances), which are an index of lipid peroxidation in oxidative stress. However, sparing of plasma antioxidants, ascorbic acid and α -tocopherol was not observed.

TAC is a biochemical parameter suitable for evaluating the overall antioxidant status of serum or plasma resulting from antioxidant intake and/or production, and their consumption by the normal or increasing levels of oxidative stress. Therefore, measuring TAC can also be applied to optimize and monitor antioxidant therapy (32-36). Several methods have been developed to assess TAC of serum or plasma, because of the difficulty in measuring each antioxidant component separately and the interactions between different antioxidant components in the serum or plasma. These methods are all essen-

tially inhibition methods and differ greatly. A free radical species is generated, there is an end point at which the presence of the radical is detected, and the antioxidant capacity of the added sample the end point value by scavenging the free radical (35, 36, 54). In our study, TAC was measured using the Trolox-equivalent antioxidant capacity assay described by Miller et al. (32) and commercialized by Randox company (TAS kit).

The increase of serum TAC observed in the present study, along with the increase of plasma CoQ₁₀, was expected. The increase of the latter is ascribed to exogenous, water-soluble CoQ₁₀ that was added into the dog food. The positive, significant ($p = 0.011$) correlation between plasma CoQ₁₀ and serum TAC, found 1 hour after CoQ₁₀ supplementation, indicated the contribution of CoQ₁₀ to the TAC of canine serum at this time point. Despite the tendency of plasma CoQ₁₀ to increase, serum TAC unexpectedly decreased significantly 2 hours after basal measurements. It then increased and remained at the higher level until the end of the measuring period. TAC values from all other sampling times were in general agreement with reported data (55-58). Measuring TAC may thus help in evaluating the physiological, environmental, and nutritional factors of the redox status (36). Since TAC provides an insight into the delicate balance in vivo between oxidants and antioxidants, its decrease could be due to the increased metabolic demand after food ingestion. However, a positive correlation close to statistical significance ($p = 0.052$) was determined four hours after CoQ₁₀ supplementation, when plasma CoQ₁₀ reached its peak concentration.

Albumin is the predominant circulating antioxidant agent and, with urate and ascorbate, makes the main contribution to the TAC of human plasma (32, 35-38). Measured with the Trolox-equivalent antioxidant capacity assay, albumin was shown to contribute 28% of the TAC of human serum (35). It acts as a free radical scavenger and as a chelator of transition metals and haem (37).

Albumin concentration remained within the normal reference range and did not change significantly during the 24-hour measuring period. Clearly, the above decrease in serum TAC was not accompanied by a decrease in albumin. However, positive significant correlations between albumin and serum TAC, determined at basal measurements and 40 minutes and 1, 4 and 6 hours later, indicate that albumin is a significant contributor to the TAC of canine serum, as is the case for human serum and plasma. These

results contrast with those of Nemeč et al. (56), where no significant correlation was found between albumin and serum TAC in healthy beagle dogs, using the same method. The discrepancy could be due to the different equipment for determining TAC used in the two studies. The evidence from the performance of the TAS kit used here is that even slight changes in reaction conditions, such as temperature and run time, have marked effects on the apparent contributions of individual antioxidants, notably albumin (34, 59).

Basal biochemical measurements showed that, with the exception of alkaline phosphatase and inorganic phosphate, all biochemical parameters remained within the normal reference range (43, 44). All, except AP and Alb, differed significantly from the basal measurements during the 24-hour measuring period, with minor deviations from the normal range, which may be ascribed to the normal diurnal variations in dogs fed three times a day.

Variation of serum glucose concentration has many causes, including feeding, catecholamine release after excitement or fright, and the influence of glucocorticoid in stressed subjects. The dogs used in the present study were accustomed to the environment before the study and had been subjected to repeated venipuncture. Thus the variations are not attributable to stress (43, 60-62), but rather to feeding regime (61, 63). The diurnal urea oscillations are referable to feed intake, dietary protein supply and renal excretion (64). Variations in serum creatinine are normally related to muscle metabolism and muscle fibres in food (43, 65-67). Daily changes of electrolytes, sodium, potassium and chloride, are associated with water and food intake, excretion through skin, breathing, urine and faeces. Calcium and inorganic phosphate concentrations are influenced by renal clearance, absorption in intestine, resorption and deposition in bone, and shifting between intra and extracellular fluid compartments (43, 68, 69). These processes are under hormonal regulation that follows a diurnal pattern (70).

The mean AP values, with high standard deviations, exceeded the upper range of normal values at all sampling times on account of one dog. The slight increases in alanine aminotransferase activity observed in the present study are probably due to the liver's role in detoxification and the concomitant mild degree of hepatocyte injury (43). Albumin and all other proteins except the immunoglobulins are synthesized by the liver. These proteins are cat-

abolized in all active tissues. Diurnal fluctuations in serum proteins are due to repartition of proteins according to physiological metabolic needs (43, 71).

Haematological parameters remained within the normal reference ranges (43, 45) in basal measurements. Though all the parameters, with the exception of LUC, changed significantly over 24-hours, there were minor, but not clinically important, deviations of MCH, MCHC, NEUT and LYMPH from normal values. Most of the changes can be ascribed to normal diurnal variations. The diurnal variations in the number of circulating blood cells are the result of multiple factors, such as the distribution between the marginal cell compartment among the tissues and organs of the body, influx from storage sites, cell proliferation, release of newly formed cells into the circulation, and the destruction and removal of damaged and old cells (43, 72-74). Blood erythrocyte concentrations are established by the relative rates of erythrocyte production, shifting of erythrocytes to and from splenic sinuses, and erythrocyte destruction. Erythrocyte production depends on the degree and duration of erythropoietin stimulus and the ability of precursor cells to respond to erythropoietin (73, 75). HGB concentration in the present study was related to the number of circulating RBC. Diurnal fluctuations in blood platelet concentration depend on platelet production, consumption and destruction, and on the shifting of platelets to and from the circulation (76). Platelet production and reactivity are affected mostly by the degree of cytokine stimulation, especially thrombopoietin, interleukin 6 and erythropoietin, and the number of responsive cells (77, 78). The variation in number of total leukocytes, neutrophils, lymphocytes and eosinophils during the sampling period is attributable to the influence of environmental factors such as light, activity, feeding and handling, but might also have followed an established diurnal pattern (79).

In conclusion, the results of the present 24-hour follow-up study have established the endogenous plasma CoQ₁₀ concentration and its correlation with TAC in healthy beagle dogs. The administration of a single oral dose of 30 mg of water-soluble CoQ₁₀ resulted in a statistically significant increase of plasma CoQ₁₀, with a peak in concentration four hours after administration. TAC was not observed to increase simultaneously, however at one hour after the administration of CoQ₁₀ there was a positive, significant ($p = 0.011$) correlation between these two parameters, indicating a contribution of CoQ₁₀ to the TAC of canine serum. There was also a positive cor-

relation close to significance ($p = 0.052$) when plasma CoQ_{10} reached its peak value. Significant correlations between albumin and serum TAC, determined at basal measurements and other time points, indicate that albumin is a significant contributor to the TAC of canine serum. Selected haematological and biochemical parameters over 24-hours showed the diurnal variations normally found in dogs.

This study should be followed by a repeated-dose study in order to establish the influence of long-term administration of CoQ_{10} on TAC in dogs, particularly in terms of correlation between the TAC and the time to reach the steady-state concentration of CoQ_{10} . In addition, there is a need to establish reference values of CoQ_{10} in dogs to support further clinical studies on CoQ_{10} implementation in the treatment of various diseases.

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24-URNO SPREMLJANJE PLAZEMSKEGA KOENCIMA Q₁₀, CELOTNE ANTIOKSIDANTNE KAPACITETE IN IZBRANIH KRVNIH PARAMETROV PO ZAUŽITJU ENKRATNEGA ODMERKA VODOTOPNEGA KOENCIMA Q₁₀ PRI ZDRAVIH PSIH PASME BEAGLE

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Povzetek: Koencim Q (CoQ₁₀) je ena izmed najbolj obetavnih spojin v antioksidantni terapiji glede na njegove antioksidantne lastnosti in ključno vlogo pri delovanju mitohondrijev. Raziskave na ljudeh so pokazale pozitiven učinek CoQ₁₀ pri zdravljenju številnih bolezni. Kljub temu da je delovanje CoQ₁₀ pri ljudeh in živalih v osnovi zelo podobno, obstaja le omejeno število študij in eksperimentalnih podatkov o uporabi CoQ₁₀ pri psih. V okviru naše raziskave smo 24 ur spremljali koncentracijo plazemskega CoQ₁₀, celotno antioksidantno kapaciteto seruma (TAC – Total Antioxidant Capacity) in izbrane biokemijske in hematološke parametre pri zdravih psih pasme beagle po enkratnem zaužitju 30 mg vodotopnega CoQ₁₀. Namen raziskave je bil tudi ugotoviti morebitno povezavo med plazemskim CoQ₁₀ in serumskim TAC. Prav tako smo določili korelacije med TAC in albumini, ki so prevladujoči antioksidanti v človeški plazmi. Plazemska koncentracija CoQ₁₀ se je statistično značilno zvišala že 20 minut po dajanju CoQ₁₀ in dosegla vrh štiri ure po zaužitju CoQ₁₀. V nasprotju z našimi pričakovanji se vrednosti CoQ₁₀ in TAC nista istočasno zvečali, določili pa smo statistično značilno korelacijo med parametroma eno uro po zaužitju CoQ₁₀ ($p = 0.011$), kar kaže na prispevek CoQ₁₀ k celotni antioksidantni kapaciteti pasjega seruma. Štiri ure po zaužitju CoQ₁₀, ko je plazemska koncentracija CoQ₁₀ dosegla največjo vrednost, je bila korelacija blizu statistične značilnosti ($p = 0.052$). Pozitivne statistično značilne korelacije med TAC in albumini smo določili ob bazalnih meritvah, ter 40 minut, 1, 4 in 6 ur kasneje, kar kaže na pomemben prispevek albuminov k celotni antioksidantni kapaciteti pasjega seruma. Vrednosti izbranih hematoloških in biokemijskih parametrov so se v obdobju 24 ur spreminjale v skladu s pričakovanimi dnevnimi nihanji pri psih.

V nadaljevanju bi bilo potrebno raziskati vpliv dolgotrajnega dajanja CoQ₁₀ na TAC pri psih.

Ključne besede: koencim Q₁₀; celokupna antioksidantna kapaciteta; psi