BioFactors

Research Communication

The reduced form of coenzyme Q10 improves glycemic control in patients with type 2 diabetes: An open label pilot study

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Abstract.

Coenzyme Q10 (CoQ10) provides the energy for vital cellular functions and is known to act as an antioxidant. We conducted an open label study to examine the clinical effects of supplementation of the reduced form of CoQ10, ubiquinol, in addition to conventional glucose-lowering agents in patients with type 2 diabetes. Nine subjects (3 males and 6 females) with type 2 diabetes and receiving conventional medication were recruited. The subjects were assigned to receive an oral dose of 200 mg ubiquinol daily for 12 weeks. The effect of ubiquinol on blood pressure, lipid profile, glycemic control, oxidative stress, and inflammation were examined before and after ubiquinol supplementation. In addition, five healthy volunteers were also assigned to receive an oral dose of 200 mg ubiquinol daily for 4 weeks to examine the effects of ubiquinol on insulin secretion. In patients with diabetes, there were no differences with respect to blood pressure, lipid profile, oxidative stress marker, and inflammatory markers. However, there were significant improvements in glycosylated hemoglobin (53.0 $\pm$ 4.3 to 50.5 $\pm$ 3.7 mmol/mol, $P = 0.01$) (7.1 $\pm$ 0.4 to 6.8 $\pm$ 0.4%, $P = 0.03$). In healthy volunteers, the insulinogenic index (0.65 $\pm$ 0.29 to 1.23 $\pm$ 0.56, $P = 0.02$) and the ratio of proinsulin to insulin were significantly improved (3.4 $\pm$ 1.8 to 2.1 $\pm$ 0.6, $P = 0.03$). The results of our study are consistent with the suggestion that the supplementation of ubiquinol in subjects with type 2 diabetes, in addition to conventional antihyperglycemic medications, improves glycemic control by improving insulin secretion without any adverse effects.

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1. Introduction

Coenzyme Q10 (CoQ10) is a key component of mitochondrial oxidative phosphorylation and adenosine triphosphate production [1], and it has also been reported that CoQ10 protects mitochondrial membrane proteins and lipids, as well as DNA, from oxidative damage. CoQ10 exists in microorganisms, plants, and animals, and it is present in a reduced form (ubiquinol) and an oxidized form (ubiquinone) in the human body. Ubiquinol is the most common form of CoQ10 in the body and provides the anti-oxidant effect. While usually more than 95% of the total CoQ10 in the plasma consists of ubiquinol [2], it has been reported that the amount of ubiquinol decreases in certain conditions, especially in aging and diabetes [3,4].

The incidence of type 2 diabetes has increased worldwide. It has been reported that oxidative stress causes and exacerbates diabetes [5,6], and the reduction of oxidative stress might prevent diabetes and diabetic vascular complications [7,8].

CoQ10 has already been widely used for various diseases such as heart failure [9,10], Parkinson's disease

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Table 1
Subject background characteristics and demographic data

Variable	Baseline
Males/females	3/6
Age (y)	61 (7.0)[a]
Weight (kg)	60.1 (7.9)[a]
BMI (kg/m^2)	25.1 (3.5)[a]
Medication (%)	
Glucose-lowering agents	
Insulin	1 (11)[b]
α-Glucosidase inhibitors	1 (11)[b]
Sulfonylureas	4 (44)[b]
Biguanides	4 (44)[b]
Pioglitazone	4 (44)[b]
Dipeptidyl peptidase IV inhibitors	1 (11)[b]
Anti-hypertensive agents	
Angiotensin II receptor blockers	3 (33)[b]
Calcium channel blockers	2 (22)[b]
Lipid-lowering agents	
Statins	6 (66)[b]
Ezetimibe	2 (22)[b]

[a] Mean (s.e.m.).
[b] Number (ratio).

[11,12], and liver fibrosis [13]. However, the form of CoQ10 that has been clinically used is typically ubiquinone and not ubiquinol, since ubiquinol is easily oxidized in air and large scale manufacturing has been difficult.

Recently, however, a chemical research group has succeeded in manufacturing ubiquinol that can be used clinically. To date, the clinical effects of ubiquinol have been studied in patients with advanced heart failure [10] and in patients with Down syndrome [14], but there have been no reports on the effects of ubiquinol on glycemic control in patients with diabetes.

With this in mind, we thus examined the effects of ubiquinol on glycemic control in 9 patients with diabetes when supplemented for a long treatment period of 12 weeks as an open label pilot study.

2. Materials and methods

2.1. Subjects

Nine subjects (3 males and 6 females) with type 2 diabetes and receiving medication consisting of one or more anti-hyperglycemic agents, anti-hypertensive agents and/or lipid-lowering agents were recruited for this study (Table 1). In addition, 5 healthy male subjects were also recruited to explore the mode of action of ubiquinol. Diabetes mellitus was diagnosed according to the Japan Diabetes Society criteria (fasting blood glucose $>$ 126 mg/dL, blood glucose $>$ 200 mg/dL 2-h after the administration of 75 g glucose in an oral glucose tolerance test, glycosylated hemoglobin (HbA1c) $\geq$ 6.9%, or the use of oral hypoglycemic anti-diabetic medications). The inclusion criteria were a patient age between 20 and 74 years and HbA1c concentration between 50.7 mmol/mL (6.5%) and 70.5 mmol/mL (8.4%). The exclusion criteria were an age $>$75 years, current history of myocardial infarction and/or cerebral stroke, serum creatinine $>$150 μmol/L, abnormal liver or muscle enzymes, and the use of antioxidants.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and was approved by an ethical committee of the School of Medicine, Chiba University prior to its inception. All patients and healthy volunteers understood the study aims and methods and provided written informed consent.

2.2. Study design

Subjects with diabetes were administered 200 mg of ubiquinol (Kaneka, Osaka, Japan) in four 50-mg tablets daily in the morning for 3 months while the five healthy subjects were administered 200 mg of ubiquinol daily for 1 month, and the main effects on glycemic control were evaluated before and after the intervention with ubiquinol.

Meal tests were performed for healthy volunteers before and after ubiquinol administration. In the meal test, after an overnight fast, subjects were consuming meal E460F1 (460 kcal; Kewpie, Japan), comprising 56.5 g of carbohydrate, 18 g of protein, and 18 g of fat. Blood samples were drawn before the start of meal test and 30, 60, and 120 min after ingestion.

2.3. Blood pressure and brachial-ankle pulse wave velocity (baPWV)

Blood pressure and baPWV were measured at baseline and at the end of the intervention using a Dinamap 1946X/P (Omron, Japan) and a BP203RPEII for baPWV (Colin, Japan).

For blood pressure measurement, the subjects rested in the supine position for 5-min, after which the blood pressure and heart rate were then measured on the dominant arm at 2-min intervals. The mean of all blood pressure measurements was subsequently calculated.

2.4. Biochemistry

Venous blood samples were collected at baseline and at the end of the intervention in the morning after a 12-h fast. Urine samples were also collected at baseline and at the end of the intervention. For tests that were not carried out immediately, the serum and plasma, which were collected in lithium heparin tubes, were frozen at -80°C and thawed immediately prior to analysis.

The plasma ubiquinol concentration was measured by reverse-phase high-performance liquid chromatography (HPLC) using electrochemical detection. The HPLC system comprises a separation module (Model 2695, Waters Corp.), a pump (Model PU-980, JASCO Corp.), an electrochemical detector (ECD; Model SI-2, Shiseido Co., LTD.), an analytical column (YMC-Pack ODS-A [A303], 250 $\times$ 4.6 mm i.d.), and a

Table 2
Individual values at baseline and at the end of the intervention for patients with type 2 diabetes

									Ubiquinol (nmol/L)		GA (%)		HbA1c (%)	
Gender	Age	Statin	Insulin	α-GI	SU	BG	PGZ	DPPIV-I	Baseline	Post	Baseline	Post	Baseline	Post
Female	61	+	−	−	+	−	−	−	1238.0	4527.0	23.2	18.4	7.9	7.6
Female	66	+	−	−	−	−	−	−	708.0	6893.0	16.1	15.1	6.7	6.5
Male	61	+	−	−	+	+	+	−	505.0	2424.0	20	17.6	6.9	6.6
Female	63	+	+	+	−	+	+	−	723.0	1855.0	16	14.2	7.2	6.7
Female	57	+	−	−	−	−	−	−	1136.0	5860.0	16.3	17.1	6.9	7.0
Male	49	+	−	−	−	+	−	−	1743.0	19260.0	20	20.1	7.1	7.2
Female	64	−	−	−	+	−	+	−	939.0	6224.0	19.5	16.3	6.6	6.6
Male	75	−	−	−	−	−	+	−	1445.0	3920.0	21	17.8	7.1	6.7
Female	61	−	−	−	+	+	−	+	1674.0	6977.0	22.8	23.2	7.6	7.0

α-GI, α-Glucosidase inhibitors; SU, sulfonylureas; BG, biguanides; PGZ, pioglitazone; DPPIV-I, dipeptidyl peptidase IV inhibitors

reduction column (Model 21211 RC-10, Shiseido Co., LTD.). ECD was 600 mV, and the mobile phase was 50 mM $NaClO_4$ in MeOH/EtOH = 35/65 (v/v) with a flow rate of 0.6 ml/min. Quality control tests were performed on a day-to-day basis for the detection limit, linearity, recovery, accuracy, range of determination, stability of ubiquinol in the extraction fluid, and specificity and reproducibility during the day.

2.5. Statistics

For statistical comparisons, the paired *t*-test or Wilcoxon signed rank-sum test was used according to distribution. Statistical analyses were performed using SPSS 15.0J (SPSS Japan, Tokyo, Japan). Results with $P < 0.05$ were considered statistically significant.

3. Results

3.1. Ubiquinol improved glycemic control in patients with diabetes

Patients with diabetes were treated with 200 mg of ubiquinol daily for 12 weeks. All patients tolerated ubiquinol well and there were no adverse side effects, with some patients also showing improved bowel movements. Compliance was examined by interview at each hospital visit. The plasma concentration of ubiquinol was significantly increased 2 weeks after the start of administration (1123.4 ± 440.6 to 6437.8 ± 5152.5 nmol/L, $P < 0.01$) and returned to basal levels 2 weeks after administration had finished. There was no difference in the plasma concentration of ubiquinol with or without taking statins (Table 2). There were also no differences in the blood pressure, baPWV, renal function, and serum lipids before and after the intervention, as shown in Table 3. However, there were significant improvements in glycoalbumin (GA) and HbA1c, while fasting immunoreactive insulin (IRI) also tended to increase after ubiquinol administration (Table 3).

To determine how ubiquinol improved glycemic control, we calculated HOMA-R (a marker for insulin resistance) and HOMA-β (a marker for insulin secretion), and measured the levels of lipoprotein lipase (a marker for insulin resistance), malondialdehyde low-density lipoprotein (MDA-LDL, a marker for oxidative stress), and high-sensitivity C-reactive protein (a marker for inflammation); however, none of these markers were significantly different before and after the intervention with ubiquinol (Table 3). For unknown reasons, one of the nine patients in the study had extraordinarily high levels of CRP before ubiquinol administration and was excluded from the statistical analysis of CRP levels.

3.2. Ubiquinol improved insulin secretion in the healthy subjects

To determine how ubiquinol improved glycemic control, we administered 200 mg of ubiquinol daily to five healthy volunteers for 4 weeks. Meal tests were performed before and after the treatment period, and insulin secretion and Glucagon-like peptide-1 (GLP-1) were examined. As shown in Table 4, the insulinogenic index was significantly increased while the proinsulin to insulin ratio was significantly reduced after ubiquinol treatment, indicating that the administration of ubiquinol improved insulin secretion. We also examined the effects on GLP-1 secretion, however no significant differences were observed before and after treatment with ubiquinol (data not shown).

4. Discussion

In this study, we showed that ubiquinol, a reduced form of CoQ10, significantly improved glycemic control in patients with type 2 diabetes when it was supplemented in addition to conventional glucose-lowering drugs such as sulfonylureas, biguanides, pioglitazones, and insulin, while in healthy volunteers it improved insulin secretion. These results raise the possibility that the dose or number of

Table 3
Mean values of laboratory parameters at baseline and at the end of the intervention for patients with type 2 diabetes that completed the study

Variable	Baseline	Post	*P* value
Fasting blood glucose (mol/L)	7.3 (1.2)[a]	8.1 (2.1)[a]	0.161
HbA_{1c} (mmol/mL, IFCC)	53.0 (4.3)	50.5 (3.7)	0.01*
HbA_{1c} (%, DCCT)	7.1 (0.4)	6.8 (0.4)	0.03*
GA (%)	19.4 (2.8)	17.8 (2.7)	0.014*
IRI (μU/mL)	8.7 (3.4)	11.6 (6.7)	0.071
TC (mmol/L)	4.9 (1.3)	4.9 (1.6)	0.488
TG (mmol/L)	1.5 (0.7)	1.3 (0.2)	0.211
HDL-C (mmol/L)	1.4 (0.2)	1.4 (0.2)	0.5
Systolic blood pressure (mmHg)	143 (28)	142 (31)	0.385
Diastolic blood pressure (mmHg)	80 (12)	79 (13)	0.33
ba PWV (right) (%)	1748 (358)	1815 (410)	0.344
ba PWV (let) (%)	1732 (321)	1775 (338)	0.2
eGFR (mL/min)	85.1 (21.5)	84.4 (16.2)	0.08
Cystatin C (ng/mL)	0.97 (0.19)	0.96 (0.2)	0.192
Urinary albumin excretion (mg/g·cre)	46.8 (91.8)	83.2 (176.6)	0.153
HOMA-R	2.9 (1.2)	3.5 (0.1)	0.1
HOMA-β	50.2 (23)	73.5 (98)	0.21
Lipoprotein lipase (ng/mL)	61.6 (7.6)	65.6 (29.4)	0.13
MDA-LDL (U/L)	107.2 (39.6)	98.3 (29.4)	0.2
High sensitive CRP (mg/L)	837.8 (983)	942.5 (808)	0.49

Results are means (s.e.m.). GA, glycoalbumin; IRI, immunoreactive insulin; TC, total cholesterol; TG, triglycerol; HDL-C, high-density lipoprotein; baPWV, brachial-ankle pulse wave velocity; HOMA-R, homeostasis model assessment as an index of insulin resistance; HOMA-β, homeostatic model assessment beta cell function; MDA-LDL, malondialdehyde low-density lipoprotein.
*** Indicates a significant difference ($P < 0.05$).**
[a] Mean (s.e.m.).

drugs required to control blood glucose levels in patients with type 2 diabetes may be reduced with ubiquinol supplementation.

CoQ10 is a lipid-soluble molecule that is synthesized de novo in all tissues and was first isolated from beef mitochondria in 1957. CoQ10 is heterogeneously distributed among tissues, with the highest concentrations found in the heart, liver, kidney, and pancreas [15–17]. The levels in the pancreas are the highest at 1 year of age in humans and then subsequently decreases thereafter [3]. The main function of CoQ10 is in the proper transfer of electrons within the mitochondrial oxidative respiratory chain to produce adenosine triphosphate, which provides the energy for vital cellular functions such as metabolism (biosynthesis of proteins, fat, glycogen, nucleic acids, production of heat, etc.), muscle movements and neural transmission. In the antioxidant active form, CoQ10 as ubiquinol also prevents lipid peroxidation. Because of its essential role in the body, CoQ10 has been widely used in the treatment of various diseases including diabetes.

Diabetes is a chronic metabolic disorder that is characterized by hyperglycemia resulting from absolute or relative deficiencies in insulin secretion and/or insulin action. It has been reported that hyperglycemia in diabetes results in oxidative stress though an increase in reactive oxygen species (ROS) production and a decrease in ROS scavenging [18,19]. Antioxidant therapy has been shown to reduce or retard the damaging effects of ROS in diabetes and diabetic complications, although the effects of antioxidant therapy in diabetes have not yet been clarified in a clinical setting [20]. CoQ10 is supposed to function as a natural antioxidant in the body; however, it has been reported that the plasma concentrations of CoQ10 in patients with diabetes are reduced [21,10]. Therefore, the supplementation of CoQ10 in patients with diabetes is thought to be effective for preventing and retarding the development of diabetes.

A few studies have investigated the effects of ubiquinone, an oxidized form of CoQ10, in diabetes, but the results have been controversial. Three earlier randomized control trials in patients with type 1 or type 2 diabetes who received 100–200 mg/day of ubiquinone for 3–6 months failed to show an improvement in glycemic control [22,23].

Conversely, Hodgson et al. recently reported a randomized control trial that used 200 mg ubiquinone daily for 12 weeks where ubiquinone supplementation was found to have significantly improved HbA1c [24]. The lack of consistent effects of ubiquinone on glycemic control may be attributed to differences in study subjects' characteristics

Table 4
Mean values at baseline and at the end of the intervention for parameters related to glycemic control in healthy volunteers

Variable	Baseline	Post	*P* value
Fasting blood glucose (mol/L)	5.0 (0.3)[a]	5.4 (0.6)[a]	0.1
IRI (μU/mL)	3.7 (2.3)	6.0 (2.2)	0.09
HOMA-R	0.8 (0.6)	1.5 (0.5)	0.07
HOMA-β	54 (32)	66 (34)	0.31
Insulinogenic index	0.65 (0.29)	1.23 (0.56)	0.02*
Proinsulin (pmol/L)/ insulin (μU/ml) ratio	3.4 (1.8)	2.1 (0.6)	0.03*

Results are means (s.e.m.).
*** Indicates a significant difference ($P < 0.05$).**
[a] Mean (s.e.m.).

including age, BMI of patients, and baseline values of HbA1c, as well as in study conditions such as the dose of ubiquinone and standard medications used. In addition, the relatively mild effect of ubiquinone on glycemic control compared to hypoglycemic anti-diabetic drugs might also cause such inconsistent results.

While several CoQ10 products are available on the market, their absorption through the intestine, tissue uptake, and pharmacokinetics are quite different [1]. CoQ10 has thus far been used in clinical settings in its oxidized form (ubiquinone), but because the effects of CoQ10 as an anti-oxidant are actually derived from its reduced form (ubiquinol), ubiquinone must first be converted to ubiquinol after it is administered. Although it has been reported that ubiquinone is converted to ubiquinol when it is absorbed through the intestine, there are reports that showed that the ratio of ubiquinol to ubiquinone is actually reduced in diabetes [4], presumably as a result of an impairment of the conversion from ubiquinone to ubiquinol. Ubiquinol is also endowed with a better bioavailability compared to ubiquinone. Therefore, the direct supplementation of ubiquinol rather than ubiquinone in diabetes should be favorable. To our knowledge, the present study is the first to report that ubiquinol improves glycemic control in patients with type 2 diabetes. Chronic hyperglycemia results in diabetic complications through the formation of advanced glycation end products (AGEs), which are irreversibly formed biochemical end products of nonenzymatic glycation [25]. The effects of ubiquinol on glycemic control might thus also contribute to the attenuation of diabetic complications by inhibiting the formation of AGEs, although this possibility has yet to be confirmed by large and longer-term clinical studies.

We also investigated how ubiquinol improved glycemic control. As ubiquinol functions as an antioxidant, we examined the levels of MDA-LDL, a marker of oxidative stress, before and after the administration of ubiquinol but were unable to detect a significant difference. This result is consistent with the data reported by Hodgson et al. [24], who examined the levels of plasma F2-isoprostane, another marker for oxidative stress, and observed no differences before and after the administration of ubiquinone. Recently, it has been reported that ubiquinol also acts as an anti-inflammatory agent [26]. Given that chronic, persistent inflammation has a pivotal role in the development of diabetes, we examined the effects of ubiquinol on various inflammatory markers. We were not able to detect a difference in the levels of high-sensitivity C-reactive protein, interleukin-6 (data not shown), and tumor necrosis factor alpha (data not shown) before and after the administration of ubiquinol. There were also no effects on insulin resistance.

Because CoQ10 has been reported to improve beta-cell function via increased ATP production [27], we examined the effect of ubiquinol on insulin secretion in healthy volunteers. Surprisingly, we found that the supplementation of ubiquinol enhanced insulin secretion significantly in healthy volunteers, although there was less oxidative stress and inflammation in healthy volunteers compared to the diabetic subjects.

These data indicate that ubiquinol probably improves beta-cell function in insulin production and/or insulin secretion through activating mitochondrial ATP production in the cells.

There are several limitations to this study. Our study was not a randomized placebo-controlled trial (RCT) and had a relatively small sample size. Therefore, the effects of ubiquinol need to be further confirmed by RCTs with a larger population and over a longer period.

In conclusion, the results of our study are consistent with the suggestion that the supplementation of ubiquinol in subjects with type 2 diabetes, in addition to conventional antihyperglycemic medications, improves glycemic control without any adverse effects. Large population-based RCTs are necessary to define the benefits of ubiquinol use in the future.

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