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Effects of Pyrroloquinoline Quinone Disodium Salt Intake on the Serum Cholesterol Levels of Healthy Japanese Adults

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Summary Pyrroloquinoline quinone (PQQ) is a water-soluble quinone compound that has a strong anti-oxidant capacity. A previous study in rats fed a PQQ-depleted diet showed that elevated levels of serum triglyceride (TG) decreased after PQQ supplementation. However, there is only one study reporting the effects of PQQ on serum lipid levels, such as those of TG and cholesterol, in humans. In this study, the effects of PQQ disodium salt (BioPQQ^{TM}) on serum TG and cholesterol levels in humans after 6 and 12 wk of treatment at an oral dosage of 20 mg/d were examined. This trial was conducted according to a randomized, placebo-controlled, double-blinded protocol. A total of 29 healthy Japanese adults, ranging from 40 to 57 y old, with normal to moderately high TG levels (110–300 mg/dL) as measured by a recent blood examination, were included in this study. In eleven volunteers out of 29, serum low-density lipoprotein cholesterol (LDL-chol) levels at baseline were high (≥140 mg/dL). After 12 wk, the mean serum TG levels had not changed; however, a marginally significant decrease in the mean LDL-chol (from 136.1 to 127.0 mg/dL) was observed in the PQQ group. In the stratification analysis of the high LDL-chol subgroup (baseline LDL-chol level ≥140 mg/dL), the mean LDL-chol levels decreased significantly from the baseline values in the PQQ group compared to the placebo group. Our study findings suggest that PQQ suppressed the LDL-chol level, which is an important finding, because a high level of this lipid is a risk factor for various lifestyle-related diseases.

Key Words pyrroloquinoline quinone, LDL-cholesterol, human study, double-blinded, supplement

Pyrroloquinoline quinone (PQQ) is a water-soluble quinone compound, and has a strong anti-oxidant capacity (*1*, *2*). Trace amounts of PQQ are present in everyday foods and beverages (*3*) and in the organs and tissues of humans and rats (*4*). The nutritional importance of PQQ was suggested after a study on rats showed poor growth, osteolathyrism, and friable skin due to a lack of PQQ (5). In addition, several studies in humans have suggested that PQQ plays a role in cognitive improvement (*6*, *7*) and has anti-stress effects (*8*). A recent study reported that dietary PQQ alters indicators of inflammation and mitochondrial-related metabolism in human subjects (*9*).

Owing to its strong anti-oxidative properties, PQQ is likely to protect mitochondria against damage from reactive oxygen species. Aerobic respiration in the mitochondria leads to the production of reactive oxygen species, which in turn, leads to the induction of lipid peroxidation and the inactivation of lipid metabolism (*10*, *11*) through a deterioration of the mitochondrial energy production cycle. Therefore, the protection of mitochondria from oxidative stress may maintain normal metabolism in mitochondria. AMP-activated protein kinase (AMPK) that accelerates catabolism, i.e. the production of ATP, through the generation of mitochondria, activation of the glycolytic pathway, or glucose capture, is activated following PQQ ingestion in animal studies (*12*, *13*). A previous study in rats fed a PQQ-depleted diet reported that PQQ treatment led to an increase in the number of mitochondria in cells and a normalization of elevated triglyceride (TG) levels in circulating blood (*13*). It is well known that to maintain serum lipid levels at normal range is important, as excessive lipid levels are regarded as a risk factor for various lifestyle-related diseases. Although similar effects are to be expected in humans, to date, to the best of our knowledge, there is only one study on the relationship between PQQ and lipid metabolism in healthy young humans with the normal range of blood lipid levels (*9*). In the paper, the blood lipid levels remained within the normal range after taking PQQ. The primary purpose of our study was to examine the effects of continuous PQQ treatment for 12 wk on human lipid levels in a randomized, double-blinded, placebo-controlled trial. The volunteers in this study were healthy Japanese adults with normal to moderately high TG levels including those who had normal to high low-density lipoprotein cholesterol (LDL-chol) levels.

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Table 1. Ingredients of the test materials.

	PQQ		Placebo	
Form	Hard capsule		Hard capsule	
	PQQ[1]	10 mg	Starch	187 mg
	Starch	150.5 mg	Caramel coloring	8.8 mg
	Calcium stearate	7.5 mg	Calcium stearate	11 mg
	Starch hydrolysis material	82 mg	Starch hydrolysis material	13.2 mg

PQQ, pyrroloquinoline quinone.
[1] As pyrroloquinoline quinone disodium salt (BioPQQ™, manufactured by Mitsubishi Gas Chemical Co., Inc.).

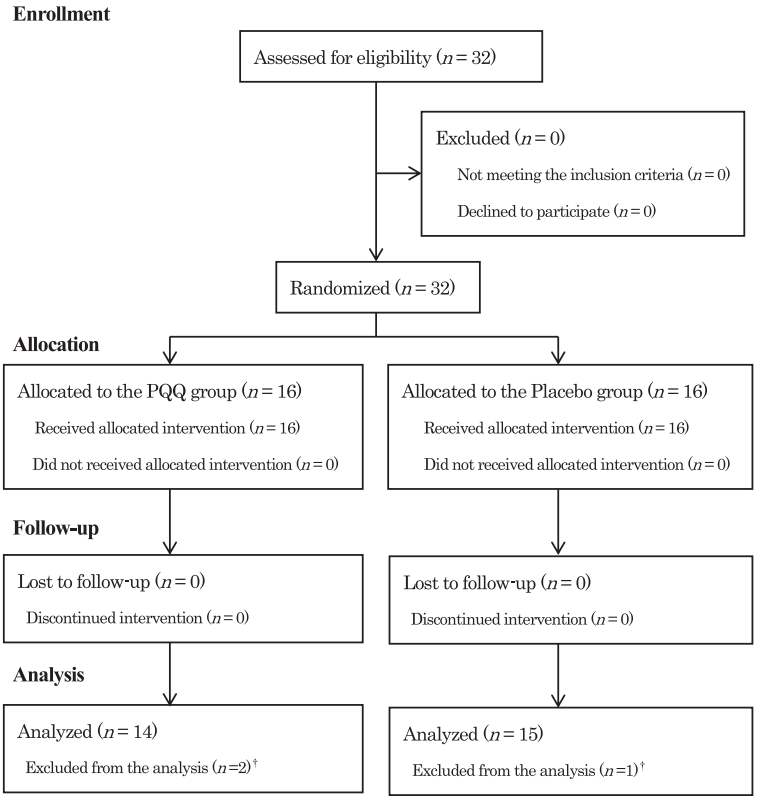

Fig. 1. Study profile. PQQ, pyrroloquinoline quinone. † Excluded from the analysis as outliers, because their triglyceride levels were statistically rejected by Thompson's rejection test.

MATERIALS AND METHODS

Participants and test materials. This trial was performed in accordance with the Helsinki Declaration (October 2000), and was approved by the institutional review board of the Seishin-kai, Takara Medical Clinic, Tokyo, Japan (chairman: Tsuyoshi Takara, M.D.; No: 1203-1202-MB01-01-TC). Japanese adults were selected on the basis of the following criteria: (a) aged between 40 and 60 y and (b) TG levels between 110 and 300 mg/dL for the 12 mo prior to the start of the study (It is indicated that a level of TG >300 mg/dL is a level which should receive consultation as a lipid abnormality in "Standard Medical Checkup and Health Guidance Program (revised edition)" (2013) published by the Ministry of Health, Labour and Welfare (*14*)). The following people were excluded: (a) those with a medical history of heart failure or myocardial infarction; (b) those undergoing treatment for atrial fibrillation, arrhythmia, liver disease, kidney disease, cerebrovascular disorder, rheumatism, diabetes, abnormal lipid disorder, hyperpiesia, or other chronic diseases; (c) those taking any other form of medication (including Chinese herbal medicines); (d) those with an allergy (to foods and/or medicines related to the test substances); (e) those taking supplements; (f) smokers; (g) those who exercised regularly; (h) those who were pregnant or possibly pregnant; (i) those who had participated in another clinical test in the 3 mo prior this study or during the test period; and (j) those who were assessed as being inappropriate for the test by a responsible physician. Participants in this study were recruited by Orthomedico, Inc. (Tokyo, Japan) and had no relationship with the Mitsubishi Gas Chemical Company, Inc. (Tokyo, Japan). Participants

Table 2. Participants' characteristics.

	All	PQQ	Placebo	*p* value[1] (PQQ vs. Placebo)
n	29	14	15	—
Male	19	9	10	—
Female	10	5	5	—
Age (y)	49.2±4.8	49.3±5.1	49.2±4.7	0.963
Height (cm)	168.2±9.1	169.5±9.4	167.0±8.9	0.475
Weight (kg)	77.8±19.8	76.2±23.2	79.2±16.8	0.691
Body fat (%)	28.6±7.0	27.4±7.9	29.7±6.2	0.387
BMI (kg/m^2)	27.2±5.3	26.2±5.8	28.2±4.8	0.319
Total-chol (mg/dL)	220.9±35.5	223.1±26.8	218.9±42.9	0.757
HDL-chol (mg/dL)	52.3±12.5	55.1±10.7	49.7±13.7	0.246
LDL-chol (mg/dL)	136.8±28.8	136.1±22.6	137.5±34.4	0.903
TG (mg/dL)	159.5±45.7	154.7±40.5	163.9±51.1	0.593

PQQ, pyrroloquinoline quinone; BMI, body mass index; chol, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides.
Data are displayed as mean value±standard deviation. [1] *t*-test.

Table 3. Comparison of end-points within PQQ and placebo groups.

	PQQ *n*=14	*p* value (vs. baseline)	Placebo *n*=15	*p* value (vs. baseline)
Total-chol (mg/dL)				
Baseline	223.1±26.8		218.9±42.9	
6 wk	214.2±20.3	0.164	220.6±39.6	0.925
12 wk	214.6±28.8	0.186	223.9±39.4	0.520
HDL-chol (mg/dL)				
Baseline	55.1±10.7		49.7±13.7	
6 wk	55.1±10.8	1.000	53.5±12.1	0.002*
12 wk	56.4±13.0	0.512	52.7±12.5	0.014*
LDL-chol (mg/dL)				
Baseline	136.1±22.6		137.5±34.4	
6 wk	129.4±16.6	0.226	139.3±33.9	0.864
12 wk	127.0±20.0	0.079†	141.0±31.2	0.565
TG (mg/dL)				
Baseline	154.7±40.5		163.9±51.1	
6 wk	151.4±41.7	0.942	142.6±49.5	0.059†
12 wk	155.9±50.7	0.992	155.8±52.7	0.603
Body fat (%)				
Baseline	27.4±7.9		29.7±6.2	
6 wk	28.7±7.7	0.382	30.3±6.4	0.157
12 wk	27.2±8.2	0.837	30.5±6.0	0.058†
BMI (kg/m^2)				
Baseline	26.2±5.8		28.2±4.8	
6 wk	26.3±5.7	0.57	28.3±4.8	0.775
12 wk	26.1±5.8	0.869	28.2±4.7	0.877

PQQ, pyrroloquinoline quinone; chol, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; BMI, body mass index.
Data are displayed as mean value±standard deviation. Multiple comparisons within each group were conducted using Dunnett's test. * $p<0.05$, † $p<0.10$ compared with the baseline values.

were randomly divided into two groups: the PQQ group (11 men and 5 women) and the placebo group (11 men and 5 women). Among study participants, 6 of 14 volunteers in the PQQ group and 5 of 15 volunteers in the placebo group showed high serum LDL-chol levels ≥140 mg/dL at baseline.

Table 1 shows the ingredients of the PQQ and placebo preparations. All subjects ingested two capsules of PQQ (20 mg/d as PQQ disodium salt, BioPQQ™) or a placebo per day after breakfast with lukewarm water for 12 wk. The dosage of PQQ in this study was based on our previous studies (*6–8*), which is far beyond the estimated

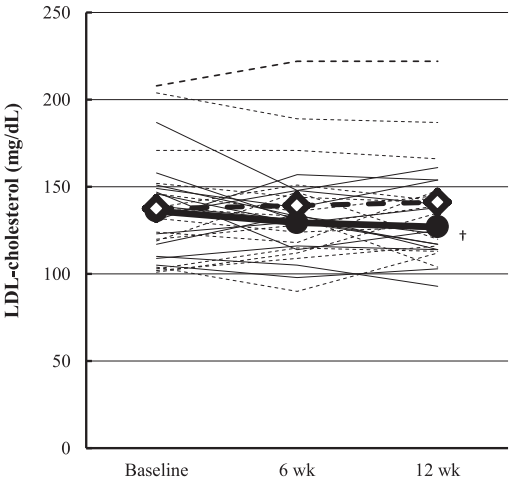

Fig. 2. Changes in serum LDL cholesterol levels for the PQQ group (n=14, solid lines) and placebo group (n=15, broken lines). The thick and thin lines show the mean values and individual values respectively. † $p<0.10$ compared with the baseline. LDL, low-density lipoprotein; PQQ, pyrroloquinoline quinone.

daily intake of PQQ from everyday foods and beverages (0.1–1.0 mg of PQQ/d) (*9*).

Measurements. All participants underwent physical examinations, and peripheral blood tests at baseline (before treatment) and at 6 and 12 wk later. Primary end-points were serum lipid levels and body composition: total cholesterol (total-chol), low-density lipoprotein cholesterol (LDL-chol), high-density lipoprotein cholesterol (HDL-chol), TG, percentage of body fat and body mass index (BMI). Secondary end-points was blood analysis parameter, which was measured for the assessment of drug safety. Blood analyses were conducted by the LSI Medience Corporation (Tokyo, Japan), and physical examinations, and peripheral blood tests were carried out at the Takara Medical Clinic (Tokyo, Japan).

Statistical analysis. The null hypotheses that there would be no differences between the baseline and 6- or 12-wk measurements, and between the PQQ group and the placebo group, were verified. When statistical significance was recognized, the null hypothesis was rejected. Significance was set at 5% (two-sided test). Multiple comparisons within a group were conducted using Dunnett's test (*15*, *16*), and comparisons between the groups were carried out by independent t-tests. Statistical analyses were conducted by a statistician at Orthomedico, Inc. using SPSS version 18.0 (SPSS Inc., Chicago, IL).

RESULTS

Figure 1 summarizes the trial progression and participant numbers. The data of three participants were excluded from the statistical analyses, because they were outliers. The exclusion was based on Thompson's rejection test (*17*) using the TG levels (547 mg/dL [$t(48)=4.85$, $p<0.001$], 422 mg/dL [$t(45)=4.43$, $p<0.001$], and 340 mg/dL [$t(48)=3.66$, $p<0.001$]). There were no other outliers using parameters besides the TG levels. During the test period, the average ingestion rate to assigned numbers of capsules was 99.1%. Table 2 shows the demographics of participants included in the analyses and the descriptive statistics of the primary and secondary end-points at baseline. No significant differences between the groups were found for any of these parameters.

Table 4. Comparison of the end-point variations between the PQQ and placebo groups.

	PQQ n=14	Placebo n=15	p value
Total-chol (mg/dL)			
6 wk	−8.9±20.4	1.7±17.9	0.153
12 wk	−8.5±20.0	5.0±21.0	0.087†
HDL-chol (mg/dL)			
6 wk	0.0±4.5	3.9±3.6	0.018*
12 wk	1.4±5.6	3.0±4.4	0.393
LDL-chol (mg/dL)			
6 wk	−6.7±19.3	1.8±12.5	0.176
12 wk	−9.1±16.8	3.7±17.1	0.052†
TG (mg/dL)			
6 wk	−3.3±42.6	−21.3±39.4	0.247
12 wk	1.2±31.2	−8.1±38.2	0.475
Body fat (%)			
6 wk	0.5±1.5	0.6±1.5	0.841
12 wk	−0.2±1.7	0.8±1.4	0.105
BMI (kg/m^2)			
6 wk	0.1±0.6	0.1±0.6	0.877
12 wk	−0.1±0.5	0.1±0.9	0.612

PQQ, pyrroloquinoline quinone; chol, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; BMI, body mass index.
Data are displayed as mean value±standard deviation. *$p<0.05$, †$p<0.10$ for comparison between the groups.

Serum lipids, percentage of body fat, and body mass index

The values for blood parameters tested, and physical measurements at 6 and 12 wk were compared with those at baseline for each group (Table 3). For the PQQ group, only LDL-chol had decreased with marginal significance at 12 wk (p=0.079; Fig. 2); however, there was no difference for any other end-point measured. Meanwhile, in the placebo group, HDL-chol increased significantly at both 6 wk (p=0.002) and 12 wk (p=0.014), and TG decreased at 6 wk with marginal significance (p=0.059); however, there was no difference at 12 wk. The percentage of body fat in the placebo group was marginally higher at 12 wk (p=0.058).

The mean deviation in each primary end-point from baseline values was compared between the two groups (Table 4). The HDL-chol level of the PQQ group at 6 wk was significantly lower than that of the placebo group (p=0.018), while the total-chol and LDL-chol at 12 wk were marginally lower in the PQQ group (p=0.087 and 0.052, respectively). There were no significant differences in the values observed for TG, percentage of body fat, or BMI between the two groups at 6 or 12 wk.

Table 5. Comparison of end-points for the high LDL-chol subgroup within the treatment groups.

	PQQ $n=6$	p value (vs. baseline)	Placebo $n=5$	p value (vs. baseline)
Total-chol (mg/dL)				
Baseline	243.7±20.5		270.0±20.2	
6 wk	215.8±12.1	0.004*	261.8±32.9	0.412
12 wk	224.7±21.2	0.036*	266.2±34.4	0.803
HDL-chol (mg/dL)				
Baseline	57.0±10.6		60.8±17.4	
6 wk	54.3±11.2	0.400	63.6±12.8	0.260
12 wk	59.2±13.4	0.529	63.4±14.0	0.302
LDL-chol (mg/dL)				
Baseline	156.3±15.6		176.2±28.8	
6 wk	132.2±11.2	0.002*	172.4±34.9	0.619
12 wk	136.3±17.9	0.008*	172.2±33.4	0.590
TG (mg/dL)				
Baseline	152.2±47.4		152.2±26.6	
6 wk	152.2±42.0	1.000	126.2±41.6	0.174
12 wk	153.8±66.1	0.993	150.4±44.8	0.988
Body fat (%)				
Baseline	27.5±9.9		31.3±3.9	
6 wk	27.2±9.8	0.790	32.1±3.8	0.157
12 wk	26.6±10.5	0.181	31.4±4.1	0.599
BMI (kg/m^2)				
Baseline	24.5±2.9		25.4±3.3	
6 wk	24.8±3.0	0.342	25.3±3.3	0.973
12 wk	24.5±3.3	0.985	25.3±3.1	0.98

PQQ, pyrroloquinoline quinone; chol, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; BMI, body mass index.
Data are displayed as mean value±standard deviation. *$p<0.05$ compared with the baseline values.

Stratification analysis

As mentioned above, the mean value of LDL-chol declined with marginal significance at 12 wk in the PQQ group; however, the coefficients of variation (ratio of standard deviation to mean value) were rather larger in the PQQ group, as shown in Table 3: 16.6%, 12.8%, and 15.7% at baseline, 6 wk, and 12 wk, respectively. Similarly, in the placebo group, the coefficient exceeded 22%. Thus, additional stratification analyses were conducted with subjects divided into two subgroups with a standard threshold value for high LDL cholesterolemia (140 mg/dL) at baseline. It is indicated that a level of LDL-chol ≥140 mg/dL is a level which should receive consultation as a lipid abnormality according to the "Standard Medical Checkup and Health Guidance Program (revised edition)" (2013) published by the Ministry of Health, Labour and Welfare (*14*). In the PQQ group, 6 participants had a level ≥140 mg/dL (high subgroup), and 8 participants had a level <140 mg/dL (low subgroup). In the placebo group, 5 participants had a level ≥140 mg/dL, while 10 had a level <140 mg/dL.

In the high subgroup of the PQQ group, the mean LDL-chol decreased significantly at 6 wk ($p=0.002$) and 12 wk ($p=0.008$) compared to the baseline values (Table 5). In addition, total-chol decreased significantly at 6 wk ($p=0.004$) and 12 wk ($p=0.036$). In contrast, for the high subgroup of the placebo group, no significant changes were observed (Table 5 and Fig. 3).

As shown in Table 6, for the high LDL-chol subgroups, LDL-chol decreased significantly at 6 wk in the PQQ group compared to the placebo group ($p=0.015$), with a marginal decrease at 12 wk. Total-chol and HDL-chol marginally decreased in the PQQ group ($p=0.081$) at 6 wk, while the percentage of body fat decreased significantly at 12 wk compared to the placebo group ($p=0.049$). The mean deviation for TG and BMI at 6 and 12 wk were not significantly different between the two groups. Meanwhile, for the low LDL-chol subgroup, there were no significant differences in any of the cholesterol levels or other end-points (data not shown).

Serum uric acid

Serum uric acid, which is regarded as an independent risk factor for lifestyle-related diseases, was also measured. In the PQQ group, serum uric acid was significantly lower at 6 wk ($p=0.003$, from 6±1.2 to 5.4±1.1 mg/dL), while in the placebo group it was significantly higher at 12 wk ($p=0.032$, from 5.8±1.3 to 6.3±1.4 mg/dL; Fig. 4).

Safety

Results of the blood tests for the assessment of PQQ safety are shown in Tables 7 and 8. No medical problems resulting from the ingestion of PQQ or the placebo were observed. The mean values of almost all parameters measured were within the normal range, although

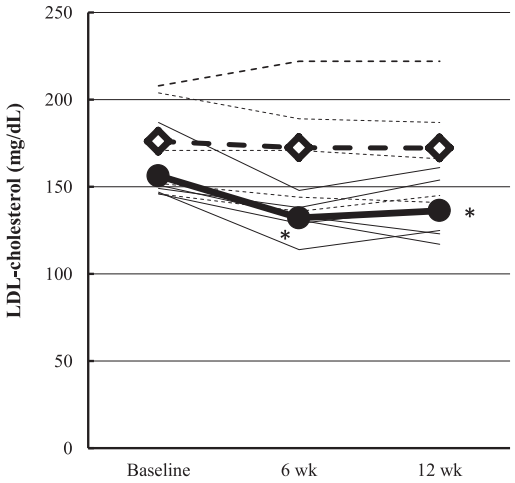

Fig. 3. Changes in the serum LDL cholesterol levels for the high LDL cholesterol subgroup (≥140 mg/dL) of the PQQ group (n=6, solid lines) and placebo group (n=5, broken lines). The thick and thin lines show mean values and individual values respectively. *p<0.05 compared with the baseline. LDL, low-density lipoprotein; PQQ, pyrroloquinoline quinone.

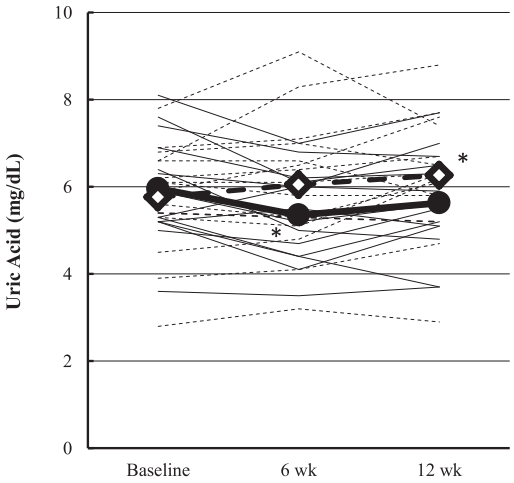

Fig. 4. Changes in the serum uric acid levels for the PQQ group (n=14, solid lines) and placebo group (n=15, broken lines). The thick and thin lines show the mean values and individual values, respectively. *p<0.05 compared with the baseline. PQQ, pyrroloquinoline quinone.

Table 6. Comparison of end-points for the high LDL-chol subgroup between the treatment groups.

	PQQ n=6	Placebo n=5	p value
Total-chol (mg/dL)			
6 wk	−27.8±12.6	−8.2±18.2	0.081†
12 wk	−19.0±18.8	−3.8±18.3	0.210
HDL-chol (mg/dL)			
6 wk	−2.7±4.2	2.8±4.7	0.079†
12 wk	2.2±6.9	2.6±4.3	0.902
LDL-chol (mg/dL)			
6 wk	−24.2±10.7	−3.8±11.3	0.015*
12 wk	−20.0±16.2	−4.0±11.7	0.091†
TG (mg/dL)			
6 wk	0.0±34.7	−26.0±32.6	0.233
12 wk	1.7±34.3	−1.8±37.8	0.878
Body fat (%)			
6 wk	−0.3±1.5	0.8±1.2	0.195
12 wk	−0.9±1.0	0.4±0.9	0.049*
BMI (kg/m^2)			
6 wk	0.3±0.6	−0.1±0.9	0.421
12 wk	0.0±0.5	−0.1±1.2	0.863

PQQ, pyrroloquinoline quinone; chol, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglycerides; BMI, body mass index.
Data are displayed as mean value±standard deviation. *p<0.05, †p<0.10 for comparison between the groups.

for several parameters there were significant changes or slight deviations. In addition, based on the result of medical history, there was no obvious deterioration in health. Moreover, no adverse events were reported by participants during the treatment period.

DISCUSSION

To the best of our knowledge, this is the first randomized, double-blinded, placebo-controlled clinical study on the effects of PQQ (at 20 mg/d for 12 wk) on the serum lipid levels, percentage of body fat, and BMI in humans. There are a couple of previous animal and human studies on the relationships between PQQ supplementation and lipid levels. In one animal study, the TG level in rats fed a PQQ-depleted diet was significantly elevated, and the level recovered to the normal range with PQQ supplementation (*13*). The modulation of mitochondrial, lipid, and energy metabolism by PQQ supplementation in rats relates to these results as underlying mechanisms (*11*). However, in a previous open-labeled human study, the TG and LDL-chol levels remained within the normal range after 48 h of PQQ supplementation in a single dose at 0.2 mg of PQQ/kg of body weight or after 72 h at 0.3 mg of PQQ/kg of body weight over 3 d. In our present human study, healthy Japanese adults with normal to moderately high serum TG levels (110–300 mg/dL) were recruited. Among our study participants, 6 of 14 volunteers in the PQQ group and 5 of 15 volunteers in the placebo group showed high serum LDL-chol levels ≥140 mg/dL at baseline. After 12 wk, the serum TG levels did not change significantly, contrary to our initial assumption; however, serum LDL-chol levels in the PQQ group decreased marginally compared to those of the placebo group. Additionally, a significant decrease was observed in the PQQ subgroup with higher baseline LDL-chol levels ≥140 mg/dL. The 140 mg/dL value corresponds to 300 mg/dL of TG from the standpoint of the threshold value of lipid abnormalities (*14*). Since it was difficult to observe the effect of PQQ in normal to moderately high TG levels, the future studies on volunteers covering wider ranges of TG or LDL-chol levels may give more obvious results. It is suggested

Table 7. Blood parameter measurements for the PQQ group.

Items, Unit	Normal range	Baseline	6 wk	12 wk
AST, IU/L	10–40	24.2±7.1	24.3±8.2	27.1±9.6
ALT, IU/L	5–45	30.0±13.6	28.0±14.6	31.9±15.8
γ-GTP, IU/L	(M/F) <80/<30	41.4±30.5	39.1±23.8	40.9±24.4
ALP, IU/L	100–325	219.4±60.5	208.8±58.8	207.3±54.6†
LDH, IU/L	120–240	181.1±23.9	184.3±24.9	191.6±33.3*
LAP, IU/L	37–61	54.3±8.9	54.4±7.7	55.6±7.1
Total bilirubin, mg/dL	0.2–1.2	0.7±0.2	0.7±0.2	0.7±0.2
Cholinesterase, IU/L	200–452	408.3±81.5	388.0±78.4	382.4±68.3†
ZTT, U	2.0–12.0	6.0±1.9	6.2±1.8	5.9±1.7
Total protein, g/dL	6.7–8.3	7.3±0.4	7.2±0.4	7.3±0.2
Urea nitrogen, mg/dL	8.0–20.0	13.3±2.6	12.4±2.2	13.4±3.4
Creatinine, mg/dL	0.47–0.79	0.80± 0.14	0.79±0.13	0.82±0.12
Creatinine kinase, IU/L	40–150	118.1±58.7	113.2±66.6	118.8±65.7
Calcium, mg/dL	8.4–10.4	9.5±0.4	9.6±0.2	9.7±0.3
Serum iron, μg/dL	(M/F) 40–200/40–180	114.5±41.2	105.1±22.3	116.4±34.3
Serum amylase, IU/dL	40–122	74.9±24.4	72.7±18.0	71.9±26.9
Glucose, mg/dL	70–109	93.6±23.6	88.6±11.9	91.2±21.4

Data are displayed as mean value±standard deviation. *$p<0.05$, †$p<0.10$ compared with baseline values.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; GTP, glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; LAP, leucine aminopeptidase; ZTT, zinc sulfate turbidity test.

Table 8. Blood parameter measurements for the placebo group.

Items, Unit	Normal range	Baseline	6 wk	12 wk
AST, IU/L	10–40	20.2±4.2	23.2±9.1	22.9±5.6
ALT, IU/L	5–45	24.3±7.7	27.9±11.8	29.7±15.4
γ-GTP, IU/L	(M/F) <80/<30	36.7±20.0	39.7±16.6	40.3±12.8
ALP, IU/L	100–325	214.9±59.1	199.7±45.4†	198.7±47.1†
LDH, IU/L	120–240	190.3±29.4	197.1±25.0	197.9±26.5†
LAP, IU/L	37–61	54.7±10.4	55.8±7.8	56.3±8.2
Total bilirubin, mg/dL	0.2–1.2	0.7±0.2	0.7±0.2	0.7±0.2
Cholinesterase, IU/L	200–452	370.0±61.0	374.9±61.7	370.4±57.7
ZTT, U	2.0–12.0	7.7±2.8	7.7±3.1	7.6±2.4
Total protein, g/dL	6.7–8.3	7.1±0.5	7.3±0.4	7.4±0.4†
Urea nitrogen, mg/dL	8.0–20.0	11.4±2.7	12.7±2.6*	13.7±2.2*
Creatinine, mg/dL	0.47–0.79	0.77±0.14	0.77±0.14	0.76±0.14
Creatinine kinase, IU/L	40–150	120.7±42.3	140.5±58.1	128.4±50.3
Calcium, mg/dL	8.4–10.4	9.4±0.4	9.5±0.3	9.6±0.3*
Serum iron, μg/dL	(M/F) 40–200/40–180	103.8±21.8	110.9±33.8	110.1±26.8
Serum amylase, IU/dL	40–122	64.4±20.9	64.5±22.8	67.2±22.3
Glucose, mg/dL	70–109	94.2±17.0	88.5±11.1	90.0±11.8

Data are presented as mean value±standard deviation. *$p<0.05$, †$p<0.10$ compared with the baseline (0 wk).
AST, aspartate aminotransferase; ALT, alanine aminotransferase, GTP; glutamyl transpeptidase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; LAP, leucine aminopeptidase; ZTT, zinc sulfate turbidity test.

that PQQ supplementation can affect lipid metabolism based on the fact that the LDL-chol and total-chol levels decreased significantly in the subgroup of the PQQ group over time. There was also a deviation in the LDL-chol and percentage of body fat in the subgroup of the PQQ group, because it decreased significantly compared to that of the placebo group. Further studies are needed to confirm our study findings, because the number of participants in our study was relatively small. In addition, studies on the mechanisms involved in this effect would be helpful; therefore, AMPK gene expression and mitochondrial activity in relation to lipid metabolism should be evaluated.

In this study, a decline in uric acid, or a suppression of uric acid levels by PQQ was suggested, although this was not considered in the initial investigative plan. However, the average uric acid levels remained within the standard range after PQQ treatment, and none of the par-

ticipants showed abnormally low uric acid levels. These findings suggest that PQQ treatment for 12 wk can reduce serum uric acid to normal physiological levels. Several studies have indicated that hyperuricemia may be a risk factor in metabolic syndrome (*18*). Our study findings suggest that PQQ may be useful for reducing such a risk factor.

This is the first clinical, double-blinded, placebo-controlled study on the effects of PQQ on serum cholesterol and uric acid levels in humans. Serum LDL-chol levels in the high subgroup decreased significantly. In addition, serum uric acid levels decreased significantly in the PQQ group. There were no safety concerns relating to our study conditions. Further studies with a larger number of participants and molecular studies are needed to clarify the underlying mechanisms of these effects.

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Declaration of interest

The authors declare no potential conflicts of interest.

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