Safety Assessment of PureSorb-Q™40 in Healthy Subjects and Serum Coenzyme Q₁₀ Level in Excessive Dosing

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Summary PureSorb-Q™40 (water-soluble type CoQ₁₀ powder, CoQ₁₀ content is 40 w/w%; hereinafter referred to as P40) is reported in the single-dose human and rat studies to have a greater absorption rate and absorbed volume of CoQ₁₀ even taken postprandially, than those of regular CoQ₁₀, which is lipid-soluble and generally taken in the form of soft-gel capsules. Thus, it was anticipated that the serum CoQ₁₀ level might be higher with P40 tablets than with soft-gel capsules, even for the same dose of CoQ₁₀. In the present study, in order to confirm the safety and measure the serum CoQ₁₀ level for the case of an excessive dose of P40, a double-blinded Placebo controlled comparative study was conducted on 46 healthy volunteers and they were randomly divided into two groups. The P40 tablets or placebo were repeatedly taken by the volunteers. As the result of the study, for the group of taking 2,250 mg/d of P40 (that is, 900 mg/d of CoQ₁₀) for 4 consecutive wk, the serum CoQ₁₀ level peaked at 2 wk after the start of intake at 8.79±3.34 µg/mL, and at 4 wk, it was at the level of 8.33±4.94 µg/mL. At 2 wk from withdrawal of intake, the serum CoQ₁₀ level decreased to 1.30±0.49 µg/mL. The serum CoQ₁₀ levels at these three points were significantly higher than those of the first day of intake and the Placebo group, which had no significant change throughout the study. Furthermore, P40 intake did not cause any significant changes in symptoms or clinical laboratory results as assessed by physical, hematological, blood biochemical or urinalysis tests. Physician examinations also did not reveal any abnormalities. These results confirm that P40 is an extremely safe material and it can produce better absorption of CoQ₁₀.

Key Words coenzyme Q₁₀, water-soluble, PureSorb-Q™40, toxicity, clinical trial

Coenzyme Q₁₀ (CoQ₁₀) is a lipid-soluble substance that plays an important role in the body as an essential factor for the mitochondrial electron transfer system, and represents a biofactor that is directly involved in the energy production system of the body (1, 2). CoQ₁₀ was first chemically synthesized in 1958 (3), and has been closely examined as a functional food material and cosmetic raw material in and outside Japan, and because of its excellent benefits and safety. CoQ₁₀ is being widely utilized (4–6). Since CoQ₁₀ is highly lipid-soluble, it is not well absorbed, and even when taken with a meal, only about 3% of administered CoQ₁₀ is absorbed (7). Due to high lipid solubility, usage in foods is limited. PureSorb-Q™40 (water-soluble type CoQ₁₀ powder, CoQ₁₀ content is 40 w/w%; hereinafter referred to as P40) is a very fine water-soluble powder with a mean particle size of approximately 0.19 µm when dispersed in water. While emphasizing its safety, P40 was developed to improve processability and absorption of CoQ₁₀ when taken without food.

A 13-wk consecutive P40 dosing study using rats (sub-acute toxicity study) showed that the nontoxic dosage of P40 in both male and female rats was 2,000 mg/kg, confirming that P40 is a highly safe food material (8). A study of single oral intake using rats and humans has shown that, compared to lipid-soluble CoQ₁₀, uptake rate and volume of CoQ₁₀ are significantly higher for P40 when administered both postprandially and in the fasting state (9). Considering this result, compared to soft-gel capsules as the common form for intake of lipid-soluble CoQ₁₀, serum CoQ₁₀ concentration is expected to be higher with P40 even at the same dose; therefore, some safety concern was anticipated. In the present study, a total of 2,250 mg/d of P40 (900 mg/d of CoQ₁₀) was administered (CoQ₁₀ 450 mg BID) after meals, in the morning and in the evening, for 4 consecutive weeks, and safety and serum concentration were assessed.

MATERIALS AND METHODS

Materials. As a test supplement, tablets containing 125 mg of PureSorb-Q™40 (which is equivalent to 50 mg of CoQ₁₀) were prepared. PureSorb-Q™40 (P40) was developed by Nisshin Pharma (Tokyo, Japan), and its ingredients are CoQ₁₀, food starch-modified, maltodextrin (tapioca) and glycerin. As the Placebo, gardenia dye and cellulose were used instead of P40, and tablets that could not be distinguished in terms of appearance...
or form were prepared. For both P40 and Placebo groups, 9 tablets (for a single dose) were placed in an aluminum bag, and 32 bags were placed in a larger aluminum bag and given to each participant.

Subjects. The present clinical study was conducted on male and female volunteers recruited at Miyawaki Orthopedic Clinic (Eniwa, Hokkaido, Japan). Participants comprised 46 healthy male and female with a mean age of 38.8 ± 1.8 y (range, 20–40 y) and mean body mass index (BMI) of 21.9 ± 0.3 kg/m² (range, 17–26) who agreed by means of written consent after being informed of the significance, methods and objective of the present study.

Protocol. Using enrolled participants, the study was conducted with approval from the Investigational Review Board (IRB) of Miyawaki Orthopedic Clinic in compliance with the ethical principles of the Declaration of Helsinki under the supervision of the chief investigator and other investigators. The present double-blinded, Placebo-controlled comparative study was conducted using tablets of 2,250 mg/d of P40 (900 mg/d of CoQ10) and Placebo tablets. The 46 screened subjects were randomly divided into 2 groups to receive either the P40 tablets (P40 group: 12 male, 11 female) or Placebo tablets (Placebo group: 11 male, 12 female). In each group, each subject took 9 tablets twice daily, after breakfast and dinner, for 4 consecutive weeks. Throughout the study period, subjects were instructed to keep an intake record and to visit the clinic a total of 4 times without eating breakfast on the day of each visit as follows: first day of intake; 2 wk after start of intake; 4 wk after start of intake; and 2 wk after end of intake (post-intake observation period). At each visit, physician examinations, physical tests, hematological and blood biochemical tests and urinalysis test were performed to confirm safety and measure serum CoQ10 concentration. The tests conducted are listed in Table 1. After the tests were completed, subjects took breakfast and the test supplement or placebo. On the day previous to each visit, subjects were instructed not to eat or drink after 21:00 except for water.

The subjects were instructed to abstain from taking drugs and dietary supplements containing CoQ10 from the time of screening to the end of the study. During the study period, subjects were also instructed to avoid marked alterations to diet or lifestyle and excessive drinking or eating.

Measurement of serum coenzyme Q10 concentration. With each blood sample, 2 mL was centrifuged at 800 × g for 10 min. then the resulting serum sample was stored frozen at −80 °C until testing. Serum CoQ10 concentration was measured using a modification of the methods of Yamamoto et al. (10) by HPLC equipped with an electrochemical detector. All forms of CoQ10 were converted to reduced CoQ10, and total serum CoQ10 concentration was determined.

Data analysis. With all numerical data, mean and standard deviation (SD) were calculated for each group. With a significance level of 5%, paired t-tests were used to compare data before and after intake. F tests were used to assess equal variance between groups, while Student’s t test was used for even variance and the Aspin-Welch t test was used for uneven variance.

RESULTS

Subjects

Before the study was initiated, it was decided that if some abnormal symptoms appeared, either subjective or objective, the subjects could withdraw from the study at any time or the chief investigator could withdraw the subjects. But while some subjective symptoms were observed, none resulted in withdrawal from the study. Determination was also made before the study that if any subjects could no longer participate in the study due to some unexpected events occurring during the study, they would be handled as a withdrawn case, but no participants were withdrawn from the study.

The average compliance rates of the Placebo and Test groups were 99.1% (92.9–100%).

Subject background and physical tests

Table 2 shows subject background and physical test findings for the study.

On the first day of intake, for the P40 group, mean values were age, 39.7 ± 12.8 y; height, 164.4 ± 8.6 cm; body weight, 59.0 ± 8.5 kg; percent body fat, 22.8 ± 5.8%; BMI, 21.8 ± 2.1 kg/m²; body temperature, 36.2 ± 0.6 °C; systolic blood pressure, 110.9 ± 11.0 mmHg; diastolic blood pressure, 69.9 ± 8.1 mmHg; and heart rate, 66.4 ± 11.7 beats/min. For the Placebo group, as of the first day of intake, mean values were age, 37.7 ± 11.3 y; height, 162.9 ± 8.4 cm; body weight, 58.5 ± 8.3 kg; percent body fat, 23.0 ± 6.2%; BMI, 22.0 ± 1.7 kg/m²; body temperature, 36.4 ± 0.5 °C; systolic blood pressure, 113.3 ± 12.3 mmHg; diastolic blood pressure, 71.4 ± 9.4 mmHg; and heart rate, 67.5 ± 10.0 beats/min. Between the P40 and Placebo groups, no significant differences in any parameters were identified.

Regarding the changes after the start of intake, for the P40 group, compared to test results of the first day of intake, percent body fat was significantly lower at 2 and 4 wk after the start of intake; body temperature was significantly higher at 4 wk after the start of intake and 2 wk after the end of intake; and heart rate was significantly lower at 2 wk after the start of intake. For the

| Test                      | Items                                                                 |
|---------------------------|----------------------------------------------------------------------|
| Physical examination      | Body weight, blood pressure, heart rate, electrocardiogram, body temperature, medical examination by interview |
| Hematology               | Leucocytes, basophils, eosinophils, neutrophils, lymphocytes, monocytes, erythrocytes, hemoglobin, hematocrit, platelets |
| Blood biochemistry        | Total protein, albumin, A/G, AST (GOT), ALT (GPT), LDH, ALP, γ-GTP, total bilirubin, creatinine, urea nitrogen, uric acid, CPK, TC, HDL-C, LDL-C, TG, Na, K, Cl, PBG, HBAlc |
| Urinalysis                | Protein, glucose, urobilinogen, bilirubin, ketone, occult blood, specific gravity, pH |
**Table 2.** Results of physical tests.

| Items                  | Group   | First day of intake | 2 wk after start of intake | 4 wk after start of intake | 2 wk after end of intake |
|------------------------|---------|---------------------|----------------------------|-----------------------------|---------------------------|
| Age                    | Placebo | 38.0±11.0           | —                          | —                           | —                         |
|                        | P40     | 40.0±13.0           | —                          | —                           | —                         |
| Heigh (cm)             | Placebo | 162.9±8.4           | —                          | —                           | —                         |
|                        | P40     | 164.4±8.6           | —                          | —                           | —                         |
| Body weight (kg)       | Placebo | 58.5±8.3            | 58.3±8.1                   | 58.5±8.1                    | 58.4±8.0                  |
|                        | P40     | 59.0±8.5            | 59.1±8.8                   | 59.4±9.0                    | 59.1±8.9                  |
| Body fat ratio (%)     | Placebo | 23.0±6.2            | 22.8±6.1                   | 22.9±6.0                    | 23.1±6.1                  |
|                        | P40     | 22.8±5.8            | 21.6±5.5**                 | 22.0±5.5**                  | 22.3±5.2                  |
| BMI                    | Placebo | 22.0±1.7            | 21.9±1.7                   | 22.0±1.7                    | 21.9±2.1                  |
|                        | P40     | 21.8±2.1            | 21.8±2.1                   | 21.9±2.1                    | 21.8±2.2                  |
| Body temperature (˚C)  | Placebo | 36.4±0.5            | 36.3±0.4                   | 36.5±0.4                    | 36.4±0.5                  |
|                        | P40     | 36.2±0.6            | 36.4±0.4                   | 36.5±0.3*                   | 36.4±0.3*                 |
| Systolic pressure (mmHg)| Placebo| 113.0±12.0         | 113.0±13.0                 | 111.0±12.0                  | 113.0±13.0                |
|                        | P40     | 111.0±11.0          | 111.0±9.0                  | 110.0±11.0                  | 114.0±10.0                |
| Diastolic pressure (mmHg)| Placebo| 71.0±9.0           | 70.0±10.0                  | 69.0±10*                    | 71.0±10.0                 |
|                        | P40     | 70.0±8.0            | 68.0±7.0                   | 69.0±7.0                    | 71.0±8.0                  |
| Heart rate (beats/min) | Placebo | 68.0±10.0           | 70.0±9.0                   | 69.0±15.0                   | 68.0±10.0                 |
|                        | P40     | 66.0±12.0           | 70.0±12.0**                | 68.0±9.0                    | 67.0±9.0                  |

Each value shows mean±SD (n=23).

*p<0.05 versus first day of intake (Paired-t).

**p<0.01 versus first day of intake (Paired-t).

Table 3–1. Results of hematology tests.

| Items                   | Group   | n   | First day of intake | 2 wk after start of intake | 4 wk after start of intake | 2 wk after end of intake |
|-------------------------|---------|-----|---------------------|----------------------------|-----------------------------|---------------------------|
| WBC (/μL)               | Placebo | 23  | 5,640±1,438         | 5,447±1,536                | 5,393±1,613                 | 5,661±2,109               |
|                         | P40     | 23  | 4,790±959*          | 4,823±963                  | 4,901±1,010                 | 5,130±1,268               |
| RBC (×10^3/μL)          | Placebo | 23  | 459±42              | 457±39                     | 457±41                      | 458±44                    |
|                         | P40     | 23  | 460±45              | 451±43*                    | 451±39*                     | 462±50                    |
| Hemoglobin (g/dL)       | Placebo | 23  | 14.1±1.5            | 14.0±1.4                   | 14.0±1.5                    | 13.8±1.4*                 |
|                         | P40     | 23  | 13.9±1.9            | 13.5±1.7**                 | 13.5±1.7**                  | 13±1.7***                 |
| Hematocrit (%)          | Placebo | 23  | 44.5±4.5            | 44.1±3.9                   | 44.0±4.3                    | 43.4±4.3**                |
|                         | P40     | 23  | 44.1±4.7            | 42.5±4.8**                 | 42.5±4.0**                  | 42.9±5.0*                 |
| MCV (fl)                | Placebo | 23  | 97.2                | 97±3                       | 96±3                        | 95±3**                    |
|                         | P40     | 23  | 96.6               | 94±2**                     | 94±6*                       | 93±7**                    |
| MCH (pg)                | Placebo | 23  | 30.7±1.1            | 30.7±1.3                   | 30.6±1.1                    | 30.2±1.1                  |
|                         | P40     | 23  | 30.1±2.8            | 30.0±2.9                   | 29.9±2.9                    | 29.2±2.7**                |
| MCHC (%)                | Placebo | 23  | 31.6±0.8            | 31.8±1.2                   | 31.9±1.0                    | 31.8±0.9                  |
|                         | P40     | 23  | 31.3±1.5            | 31.7±1.4*                  | 31.6±1.6                    | 31.4±1.0                  |
| Platelets (×10^4/μL)    | Placebo | 23  | 22.9±5.5            | 23.5±5.6                   | 22.6±5.1                    | 23.6±5.9                  |
|                         | P40     | 23  | 22.8±5.2            | 22.3±5.9                   | 22.1±4.6                    | 22.9±5.0                  |

Each value shows mean±SD.

*p<0.05 versus first day of intake (Paired-t).

**p<0.01 versus first day of intake (Paired-t).

*p<0.05 versus Placebo group (F-t test).

Placebo group, diastolic pressure was significantly lower at 4 wk after the start of intake. No other significant changes were seen in other parameters throughout the study period.

Between the P40 and Placebo groups, no significant difference was seen in any of the parameters.

**Hematology tests**

Table 3 shows the results of hematology tests.
and 2 wk after the end of intake; MCH was significantly lower at 2 and 4 wk after the start of intake. For the P40 group, RBC count was significantly lower at 2 and 4 wk after the start of intake, compared to test results of the first day of intake, for the P40/H11006/ group, RBC count was significantly lower at 2 and 4 wk after the start of intake.

Table 3–2. Results of hematology tests.

| Items                  | Group   | n  | First day of intake | 2 wk after start of intake | 4 wk after start of intake | 2 wk after end of intake |
|------------------------|---------|----|---------------------|-----------------------------|-----------------------------|--------------------------|
| Differential count of WBC |         |    |                     |                             |                             |                          |
| Baso (%)               | Placebo | 23 | 0.6±0.5            | 0.6±0.4                     | 0.6±0.4                     | 0.6±0.6                  |
|                        | P40     | 23 | 0.6±0.4            | 0.7±0.4*                    | 0.6±0.5                     | 0.5±0.3                  |
| Eosino (%)             | Placebo | 23 | 2.8±1.5            | 3.0±1.7                     | 3.0±1.5                     | 3.0±2.2                  |
|                        | P40     | 23 | 4.3±4.4            | 4.7±3.9                     | 4.8±4.7                     | 4.3±4.2                  |
| Neut (%)               | Placebo | 23 | 61.6±8.7           | 58.9±8.2                    | 61.1±9.4                    | 58.5±8.8                 |
|                        | P40     | 23 | 59.2±6.7           | 54.2±6.8**                  | 56.7±7.2                    | 54.6±9.9**               |
| Lymphocyte (%)         | Placebo | 23 | 29.6±8.6           | 32.5±8.4                    | 30.1±8.5                    | 33.0±8.1*                |
|                        | P40     | 23 | 30.8±6.1           | 35.3±7.4**                  | 32.9±7.3                    | 36.0±9.4**               |
| Mono (%)               | Placebo | 23 | 5.4±1.4            | 5.0±1.5                     | 5.3±1.5                     | 4.9±1.8                  |
|                        | P40     | 23 | 5.2±0.9            | 5.1±1.1                     | 5.2±1.2                     | 4.6±0.9*                 |

Each value shows mean±SD.
*p<0.05 versus first day of intake (Paired-t).
**p<0.01 versus first day of intake (Paired-t).
*p<0.05 versus Placebo group (t-test).

Table 4–1. Results of blood biochemistry tests.

| Items          | Group   | n  | First day of intake | 2 wk after start of intake | 4 wk after start of intake | 2 wk after end of intake |
|----------------|---------|----|---------------------|-----------------------------|-----------------------------|--------------------------|
| Total protein (g/dL) | Placebo | 23 | 7.1±0.4            | 7.2±0.4                     | 7.1±0.3                     | 7.2±0.4                  |
|                | P40     | 23 | 7.2±0.4            | 7.2±0.4                     | 7.1±0.3                     | 7.3±0.3                  |
| A/G            | Placebo | 23 | 1.57±0.16          | 1.58±0.15                   | 1.55±0.17                   | 1.57±0.17                |
|                | P40     | 23 | 1.53±0.14          | 1.54±0.14                   | 1.51±0.12                   | 1.55±0.17                |
| Albumin (g/dL)  | Placebo | 23 | 4.3±0.2            | 4.4±0.2                     | 4.3±0.2                     | 4.4±0.2                  |
|                | P40     | 23 | 4.3±0.3            | 4.3±0.2                     | 4.2±0.1*                    | 4.4±0.2*                 |
| Total bilirubin (mg/dL) | Placebo | 23 | 0.8±0.2            | 0.8±0.1                     | 0.8±0.2                     | 0.8±0.3                  |
|                | P40     | 23 | 0.8±0.2            | 0.8±0.3                     | 0.8±0.3                     | 0.9±0.3*                 |
| ASAT (U/L)     | Placebo | 23 | 17±3               | 17±2                        | 18±4                        | 17±3                     |
|                | P40     | 23 | 17±3               | 18±4                        | 17±3                        | 18±5*                    |
| ALAT (U/L)     | Placebo | 23 | 14±5               | 14±6                        | 14±4                        | 14±7                     |
|                | P40     | 23 | 13±4               | 14±7                        | 14±4                        | 14±6                     |
| ALP (U/L)      | Placebo | 23 | 207±47             | 211±45                      | 207±43                      | 215±43                   |
|                | P40     | 23 | 186±46             | 188±0                       | 185±45                      | 193±48*                  |
| LDH (U/L)      | Placebo | 23 | 163±23             | 170±22**                    | 169±25                      | 170±22*                  |
|                | P40     | 23 | 166±31             | 172±31                      | 167±28                      | 175±36                   |
| γ-GTP (U/L)    | Placebo | 23 | 18±8               | 19±9                        | 19±9                        | 20±10**                  |
|                | P40     | 23 | 19±10              | 20±10                       | 19±8                        | 21±11                    |
| CPK (U/L)      | Placebo | 23 | 99±60              | 106±66                      | 125±181                     | 108±71                   |
|                | P40     | 23 | 114±63             | 110±59                      | 124±91                      | 160±150                  |
| FBG (mg/dL)    | Placebo | 23 | 85±6              | 87±5                        | 86±6                        | 87±5                     |
|                | P40     | 23 | 86±8              | 88±6                        | 88±6                        | 88±7                     |

Each value shows mean±SD.
*p<0.05 versus first day of intake (Paired-t).
**p<0.01 versus first day of intake (Paired-t).

As to the changes after the start of intake, when compared to test results of the first day of intake, for the P40 group, RBC count was significantly lower at 2 and 4 wk after the start of intake; hemoglobin and MCV were significantly lower at 2 and 4 wk after the start of intake and 2 wk after the end of intake; MCH was significantly lower at 2 wk after the end of intake; and MCHC was significantly higher at 2 wk after the start of intake. For the Placebo group, hemoglobin, hematocrit and MCV were significantly lower at 2 wk after the end of intake. For all other parameters, no significant changes were seen throughout the study period.
Between the 2 groups, WBC count at first day of intake and Neut at 2 wk after start of intake for the P40 group were significantly lower compared to the Placebo group. For all other parameters, no significant differences were observed.

**Blood biochemistry tests**

Table 4 shows the results of blood biochemistry tests.

As to changes after the start of intake, compared to tests results of the first day of intake, for the P40 group, albumin was significantly lower at 2 wk after the start of intake, K was significantly lower at 2 and 4 wk after the start of intake, and HbA1c was significantly lower at 2 wk after the end of intake. For the Placebo group, K was significantly higher at 2 wk after the start of intake and 2 wk after the end of intake; creatinine was significantly higher at 2 wk after the start of intake, and HbA1c was significantly higher at 2 wk after the start of intake.

Between the 2 groups, uric acid level at 2 wk after the start of intake and 2 wk after the end of intake for the P40 group were significantly lower compared to the Placebo group. For all other parameters, no significant differences were observed between the 2 groups.

**Urinalysis**

Table 5 shows the results of urinanalysis.

Each symbol of the “Grade” represents as follows: (−), negative; (±), marginal; (1+), mild; (2+), moderate; (3+), severe.

For the P40 group, the following abnormal findings were observed: with qualitative protein, there was a single case of (1+) on the first day of intake; with ketone bodies, there was a single case each of (±) on the first day of intake and (1+) at 4 wk after the start of intake; and with occult blood, there was a single case each of (1+), (2+) and (3+) on the first day of intake, a single case each of (±), (1+) and (3+) at 2 wk after the start of intake, a single case of (±) at 4 wk after the start of intake, and a single case of (1+) at 2 wk after the end of intake. For the Placebo group, the following abnormal findings were observed: with qualitative protein, there was a single case of (1+) on the first day of intake, and a single case of (1+) at 2 wk after the end of intake;
with urobilinogen, there was a single case of (1+) on the first day of intake; with ketone bodies, there was a single case each of (±) and (1+) on the first day of intake and a single case of (1+) at 4 wk after the start of intake; and with occult blood, there were 2 cases each of (1+) and (2+) and single case of (3+) on the start of intake. 2 cases of (1+) and single case of (2+) at 2 wk after the start of intake, a single case of (±) at 4 wk after the start of intake, and 2 cases of (1+) and a single case of (2+) at 2 wk after the end of intake.

No deviations in other parameters or marked changes in specific gravity or pH were observed after the first day of intake.

No significant differences were observed between the 2 groups.

Table 5–1. Results of urinalysis.

| Items             | Grade | First day of intake | 2 wk after start of intake |
|-------------------|-------|---------------------|---------------------------|
|                   |       | Placebo P40         | Placebo P40               |
| Protein           | –     | 21 21 22           | 22 22                     |
|                   | ±     | 2 2 0              | 1 1                       |
|                   | 1+    | 0 0 1              | 0 0                       |
|                   | 2+    | 0 0 0              | 0 0                       |
|                   | 3+    | 0 0 0              | 0 0                       |
| Glucose           | –     | 23 23 23           | 23 23                     |
|                   | ±     | 0 0 0              | 0 0                       |
|                   | 1+    | 0 0 0              | 0 0                       |
|                   | 2+    | 0 0 0              | 0 0                       |
|                   | 3+    | 0 0 0              | 0 0                       |
| Urobilinogen      | –     | 0 0 0              | 0 0                       |
|                   | ±     | 22 23 23           | 23 22                     |
|                   | 1+    | 1 0 0              | 0 1                       |
|                   | 2+    | 0 0 0              | 0 0                       |
|                   | 3+    | 0 0 0              | 0 0                       |
| Bilirubin         | –     | 23 23 23           | 23 23                     |
|                   | ±     | 0 0 0              | 0 0                       |
|                   | 1+    | 0 0 0              | 0 0                       |
|                   | 2+    | 0 0 0              | 0 0                       |
|                   | 3+    | 0 0 0              | 0 0                       |
| Ketone            | –     | 21 22 23           | 23 23                     |
|                   | ±     | 1 1 1              | 0 0                       |
|                   | 1+    | 1 0 0              | 0 0                       |
|                   | 2+    | 0 0 0              | 0 0                       |
|                   | 3+    | 0 0 0              | 0 0                       |
| Occult blood      | –     | 18 20 20           | 20 20                     |
|                   | ±     | 0 0 0              | 0 0                       |
|                   | 1+    | 2 1 2              | 2 1                       |
|                   | 2+    | 2 1 1              | 1 0                       |
|                   | 3+    | 1 1 0              | 0 1                       |

Specific gravity 1.018±0.008 1.018±0.007 1.015±0.008 1.020±0.007

pH 6.3±0.6 6.3±1.0 6.5±0.8 6.2±0.9

ECG, subjective symptoms and examination findings by physician

Tables 6 and 7 summarize ECG findings and subjective symptoms, respectively.

Throughout the study period, no abnormalities were observed on ECG conducted for the subjects.

The following subjective symptoms were observed: for the Placebo group, rough skin was seen at 4–6 d after the start of intake, abdominal pain at 4, 6, 8 and 9 d after the start of intake, diarrhea at 10 d after the start of intake, swollen hands and face at 8 d after the start of intake, dry cough at 17–23 and 27 d after the start of intake, headache at 27 d after the start of intake and joint pain at 28 d after the start of intake (n=1 each). After the end of intake, there was a single case each of common cold at 29 d after the start of intake and headache at 30 d after the start of intake.
P40 group, common colds were observed at 3, 4, 26 and 27 d after the start of intake, stomach ache at 26 d after the start of intake, gastric discomfort at 10 and 11 d after the start of intake and headache at 3 and 8 d after the start of intake (n=1 each). No subjective symptoms were observed after the end of intake.

Physician examinations did not reveal any abnormalities for the Placebo or P40 groups.

Serum CoQ_{10} concentration

Figure 1 shows changes in serum CoQ_{10} concentration.

At the first day of intake, mean serum CoQ_{10} concentration for the Placebo and P40 groups were comparable at 0.70±0.19 μg/mL and 0.75±0.23 μg/mL, respectively. For the P40 group, compared to the first day of intake, serum CoQ_{10} concentration significantly
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peaked as 8.79 ± 3.34 μg/mL at 2 wk after the start of intake and remained significantly high at 8.33 ± 4.04 μg/mL at 4 wk after the start of intake and at 1.30 ± 0.49 μg/mL at 2 wk after the end of intake. Throughout the study period, serum CoQ_{10} concentration for the P40 group was significantly higher than that for the Placebo group in which no significant changes were observed.

**DISCUSSION**

As CoQ_{10} is a lipid-soluble substance, serum CoQ_{10} levels do not increase well when taken in the fasting state, and PureSorb-Q™40 (P40) was developed to improve processability and absorption of CoQ_{10}. In the present 4-wk intake study, 900 mg/d of CoQ_{10} was administered in the morning and at night to confirm safety and measure its serum concentration.

As the results, compared to the initial data of the first day of intake, for the data of the P40 group, some significant changes in physical tests, hematology tests, blood biochemical tests and urinalysis were observed. But the changes were transient and mild and they are within the ranges of standard values. Such similar changes were also seen for the Placebo group; therefore, the changes were considered clinically insignificant. In addition, regarding the comparison of the data between P40 group and Placebo group, a few data for the P40 group were significant lower than that of the Placebo group, such as the WBC on the first day of intake, white blood cell picture (hematology test) at 2 wk after start of intake and uric acid (blood biochemical test) at 2 wk after start of intake and 2 wk after end of intake. But, since the differences were transient and small, it is concluded that the differences were incidental and not caused by intake of the test supplement.

In urinalysis, deviations from the standard range were observed for qualitative protein levels, urobilinogen and ketone bodies, but these deviations were seen in both P40 and Placebo groups, and did not match the intake course. Furthermore, positive occult blood reactions were seen in some women starting from the first day of intake due to menstruation, and in one man in the Placebo group after the end of intake. Based on these observations, these deviations were considered as not attributable to the test supplement.

During the study period, for the P40 group, 1 man and 4 women experienced common cold, headache, stomach ache and gastric discomfort, while for the Placebo group, 4 women had rough skin, abdominal pain, swollen hands and face, diarrhea, cough and joint pain. Subjective symptoms seen for the P40 group were commonly observed in daily living, such as common colds, gastric discomfort and headache, and were sporadic and transient. Similar symptoms were also seen with the Placebo group. Furthermore, no abnormalities were observed during physician examinations. The observed subjective symptoms were thus considered not clinically significant.

As to the changes of serum CoQ_{10} concentration, compared with the first day of intake, the intake of the test supplement increased it 11-fold significantly. And the serum CoQ_{10} concentration reached a plateau at 2 wk after the start of intake. At 2 wk after the end of intake, the serum CoQ_{10} concentration decreased as only 1.7-fold of the first day of intake, and it was a significant difference compared to that of the Placebo group. This suggests, as the reduction of the serum
CoQ$_{10}$ level was remarkable, that the test supplement does not accumulate in the body. In the present study, increase of the serum CoQ$_{10}$ concentration peaked at 2 wk after the start of intake at 8.05±3.25 μg/mL. This is about 2.7-fold higher than the mean increase of serum CoQ$_{10}$ concentration (approximately 3.0 μg/mL) which was shown as the result of the repeated intake of a comparable amount of soft-gel capsules (4). Needless to say, the results can not be simply compared due to the different conditions; however, this is almost the same result as previously reported, that the serum CoQ$_{10}$ absorption rate for P40 tablets was faster than that of the soft-gel capsules, although a different dose of CoQ$_{10}$ was administered in the single dose study (9). In addition, in another study, it is reported that when 1,500 mg/d of CoQ$_{10}$ was administered repeatedly for 3 mo to Parkinson’s disease patients (11), the mean increase of serum CoQ$_{10}$ level for the study was about 5.3 μg/mL. Compared with this study, the above-mentioned result in the present study was about 1.5-fold higher. The conditions of the study on Parkinson’s disease patients were rather different from those of the present study; therefore, the comparison should be just a reference. However, it can be said the serum CoQ$_{10}$ concentration for P40, which is water-soluble CoQ$_{10}$, was markedly higher at the CoQ$_{10}$ dose of 900 mg/d, than the reported results in the other studies for the comparable and higher doses. It is suggested this result was brought about by the superior absorption of P40.

In the past studies, marked differences in the degree of increase in serum CoQ$_{10}$ concentration for the exogenous CoQ$_{10}$ have been reported. The differences might be caused due to individual differences and differing oil contents in the associated meals (12). When a single-dose of lipid-soluble CoQ$_{10}$ was administered postprandially, chenodeoxycholic acid administration increased the pool size of primary bile acid, and plasma concentration of CoQ$_{10}$ increased significantly compared to CoQ$_{10}$ administration without chenodeoxycholic acid (13). Therefore, even when taken after a meal, whether sufficient bile acid is secreted in the gastrointestinal tract for micellization of exogenous CoQ$_{10}$ is unclear. Even when lipid-soluble CoQ$_{10}$ is administered in the form of soft-gel capsules, micellization by bile acid in the small intestine is required: therefore, the above-mentioned study suggests that when a greater amount of CoQ$_{10}$ is administered, a sufficient amount of bile acid is required for adequate micellization, and it will bring about a better absorption of CoQ$_{10}$. Thus, from the perspective of micellization for intestinal absorption, because P40 is a water-soluble powder with a mean particle size of 0.19 μm when dispersed in water, micelles with particle sizes suitable for absorption are formed with markedly smaller amounts of bile acid compared to regular CoQ$_{10}$ dissolved in oil, and this brought about the higher serum CoQ$_{10}$ concentrations for the much higher dose of CoQ$_{10}$ using P40.

In order to confirm its safety and measure serum concentrations in excessive dosing of PureSorb-Q™40 (P40), a 2-group double-blinded comparative study was conducted on 46 healthy men and women. When 2,250 mg/d of P40 (900 mg/d of CoQ$_{10}$) was administered for 4 consecutive weeks, serum CoQ$_{10}$ concentration for the P40 group peaked at 2 wk after the start of intake at 8.79±3.34 μg/mL, which is 11-fold greater compared to that of the first day of intake. P40 intake did not bring any abnormal changes or abnormalities as assessed by physical, hematological, blood biochemistry or urinalysis tests. Physician examinations also did not show abnormalities. The present study thus confirmed that P40 is an extremely safe food material allowing a sufficient amount of CoQ$_{10}$ absorption.

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