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## Original article

## The effects of herring-roe lyophilized powder on lipid metabolism

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## ABSTRACT

Herring-roe, which contains large amounts of docosahexaenoic acid and eicosapentaenoic acid, has anti-dyslipidemia effects. Here, we evaluated the effects of herring-roe on lipid metabolism in 33 adult subjects in a randomized, double-blind, placebo-controlled study. We divided the subjects into a test group that ingested herring-roe lyophilized powder (herring-roe powder) and a placebo group that ingested non-herring-roe powder, with each member of each group ingesting 15 g daily for 8 weeks. Hematological tests and body composition measurements were performed before and after 4, 6, and 8 weeks of the study period. Although no significant differences in low density lipoprotein were observed, high density lipoprotein was found to be increased in subjects who ingested herring-roe powder. In addition, the level of free fatty acid was significantly improved in the herring-roe powder group. These results suggest that ingestion of herring-roe could influence lipid metabolism.

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## 1. Introduction

Over the past few decades, the prevalence of dyslipidemia has markedly increased worldwide, particularly in wealthy industrialized countries such as Japan.<sup>1</sup> Most large-scale and long-term cohort studies over the past 5–20 years have indicated that a diet rich in animal fat was associated with higher all-cause mortality.<sup>2</sup> High-fat westernized diets have been implicated in the increasing prevalence of dyslipidemia, a risk factor of atherosclerosis.<sup>3</sup> Thus, it is important to investigate the utility of functional foods and the bioactive components of food to improve and prevent dyslipidemia.

Fish oil contains rich polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).<sup>4</sup> EPA and DHA have a number of reported health benefits in humans, such as decreasing blood triglyceride concentrations in hypertriglyceremic patients and providing protective effects against

cardiovascular diseases.<sup>5</sup> This has led to recommendations from health agencies worldwide to increase dietary intake of these fatty acids.<sup>6</sup> The mechanism of DHA and EPA for improvement of lipid metabolism is the downregulation of the mature form of Sterol Regulatory Element-Binding Proteins (SREBP)-1 by decreasing SREBP-1c mRNA expression, with corresponding decreases of mRNAs of cholesterologenic and lipogenic enzymes.<sup>7</sup> In addition, DHA and EPA facilitate  $\beta$ -oxidation of fatty acid.<sup>8</sup> The Ministry of Health, Labour and Welfare recommended that adult intakes more than 1 g of DHA and EPA per day; however, dietary intake of DHA and EPA was not sufficient in Japanese people, possibly because of decreased fish intake in Japan. Thus, it is important to research functional foods to supplement DHA and EPA intake.

Herring-roe lipids contain a large amount of EPA and DHA. In addition, DHA and EPA are the major molecular constituents in the phosphatidylcholine of herring-roe.<sup>9</sup> Therefore, DHA and EPA contained in herring-roe is stable and difficult to oxidize. Moreover, herring-roe contains little cholesterol compared with that of other fish roe (260 mg cholesterol per 100 g herring-roe).

These findings suggest that herring-roe, which is rich in DHA and EPA and phosphatidylcholine-contained DHA and EPA, improves lipid metabolism. However, the clinical studies assessing herring-roe are very few. Here, we evaluated whether the ingestion of the herring-roe powder can improve dyslipidemia in an adult population.

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## 2. Methods

### 2.1. Test meal preparation and ingestion method

The composition of herring-roe powder used in this study is given in Table 1. Herring-roe was fished in Sitka, Alaska, USA. The test meal was prepared by freeze-drying in a conventional method. The production and packing was performed at Ihara Suisan Co., Ltd. (FM96883/ISO9001 certification).

The subjects were instructed to ingest 15 g per day of herring-roe lyophilized powder (herring-roe powder) (containing DHA 540 mg and EPA 300 mg) or a placebo powder (11 g of unpolished rice powder containing 4 g of soybean curd used to imitate the texture and appearance of herring-roe powder) in two parts per day.

### 2.2. Study subjects

Thirty-three volunteers (6 males and 27 females, age 40–67 years) were enrolled in this study. None had a recent history of gastrointestinal disorders, pregnancy, significant disease, surgery, severe allergic reaction to food, or current use of any medication, including anti-hyperlipidemia medication. The subjects' age, body weight, height, body mass index (BMI), and body fat percentage are listed in Table 2.

The clinical intervention was conducted as a double-blind, placebo-controlled trial. At randomization, the 33 eligible subjects were blindly assigned to one of two groups: the test group who ingested herring-roe powder and the placebo group who ingested the placebo powder. The time schedule of this clinical study is shown in Fig. 1.

We performed hematological examinations and body composition (body weight, BMI, and body fat rate) measurements at the baseline (0 week) and post-intervention (4, 6, and 8 weeks) for the two groups. The hematological examinations were consigned to Sapporo Clinical Laboratory Inc. (Sapporo, Japan). Leptin and adiponectin was measured by the Human Leptin Quantikine ELISA Kit and the Human Total Adiponectin/Acrp30 Quantikine ELISA Kit (R&D Systems, Minneapolis, MN, USA). The subjects' body composition and blood pressure were measured with an In-Body device (Biospace Co., Tokyo) and an Omron HEM-780 automatic blood pressure monitor (Omron Corp., Kyoto, Japan).

All subjects provided written informed consent prior to undergoing any study-related tests, and the protocol was approved by the Ethics Committee of Hokkaido Information University (a certificate number; 2014-01). The study protocol conformed to the Helsinki Declaration and registered at the UMIN Clinical Trial Registration System (a certificate number; UMIN000017072).

### 2.3. Statistical analysis

The average and standard deviation of age and other parameters were calculated for each group. The changes in the values of various

**Table 1**  
Composition of herring-roe powder compared with placebo powder per 15 g.

Component	Herring-roe	Placebo
Calories (kcal)	70.2	62.6
Water (g)	0.11	0.26
Proteins (g)	12.3	1.73
Lipids (g)	2.30	0.93
Carbohydrates (g)	0.09	11.8
Ash (g)	0.23	0.29
Sodium (mg)	29.6	2.06
Docosahexaenoic acid (mg)	540	–
Eicosapentaenoic acid (mg)	300	–

**Table 2**

Characteristics of the subjects in the placebo and herring-roe powder intake groups.

Characteristic	Herring-roe	Placebo	P-value
Number of subjects	n = 17	n = 16	–
Number of males (male %)	4 (76.47%)	2 (87.50%)	0.656
Age (years)	51.71 ± 9.25	53.19 ± 9.31	0.650
Height (cm)	158.43 ± 7.93	159.8 ± 5.00	0.560
Body weight (kg)	52.39 ± 9.74	58.93 ± 10.34	0.071
BMI (kg/m <sup>2</sup> )	20.73 ± 2.08	23.04 ± 3.69	0.033
Body fat percentage (%)	25.21 ± 5.42	30.18 ± 7.57	0.037

Values shown are mean ± standard deviation (SD). Statistical analysis was performed by analysis of variance (ANOVA) for age, height, body weight, and BMI, and by chi-square test for gender.

parameters were analyzed by Student's *t*-test. Statistical analyses were performed with the program IBM SPSS Statistic 19 (IBM, Armonk, NY). *P* values less than 0.05 were considered significant.

## 3. Results

### 3.1. Effects of herring-roe powder on lipid metabolism

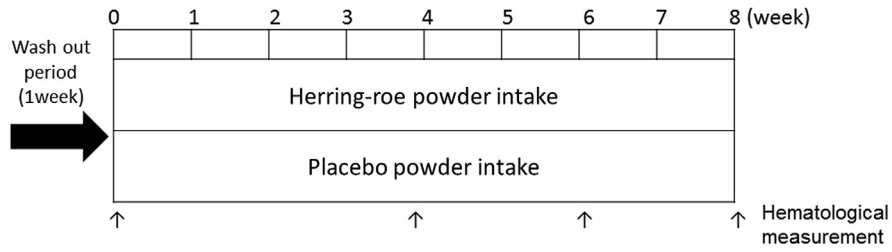
There were no significant differences in age, body weight, height, between the control and herring-roe groups (Table 2). Although BMI and body fat was significantly low in herring-roe group compared to placebo group, it did not influence the result of our clinical study. First, to determine the effect of herring-roe powder on lipid metabolism, we measured total cholesterol (T-Cho), high density lipoprotein cholesterol (HDL-Cho), LDL cholesterol (LDL-Cho), arteriosclerosis index, triglyceride (TG), nonesterified fatty acid (NEFA) (Fig. 3). T-Cho was significantly decreased by ingestion of placebo powder at the 8th week (placebo:  $-9.44 \pm 18.65$  mg/dl, herring-roe:  $4.65 \pm 11.96$  mg/dl, as the change in the level of T-Cho from baseline to 8 weeks,  $P = 0.01$ ) (Fig. 3a). However the herring-roe powder intake group improved HDL-Cho compared with the placebo powder intake group at 8 weeks (placebo:  $-1.38 \pm 5.94$  mg/dl, herring-roe:  $4.41 \pm 4.96$  mg/dl, as the change in the level of HDL-Cho from baseline to 8 weeks,  $P = 0.01$ ) (Fig. 3c). In addition, NEFA was decreased at 8 weeks by the ingestion of herring-roe powder (placebo:  $0.01 \pm 0.14$  mEq/l, herring-roe:  $-0.12 \pm 0.12$  mEq/l, as the change in the level of NEFA from baseline to 8 weeks,  $P = 0.01$ ) (Fig. 3f). There was no significant difference between the two groups of other lipid metabolism parameters.

### 3.2. Effects of herring-roe powder on adiponectin and leptin

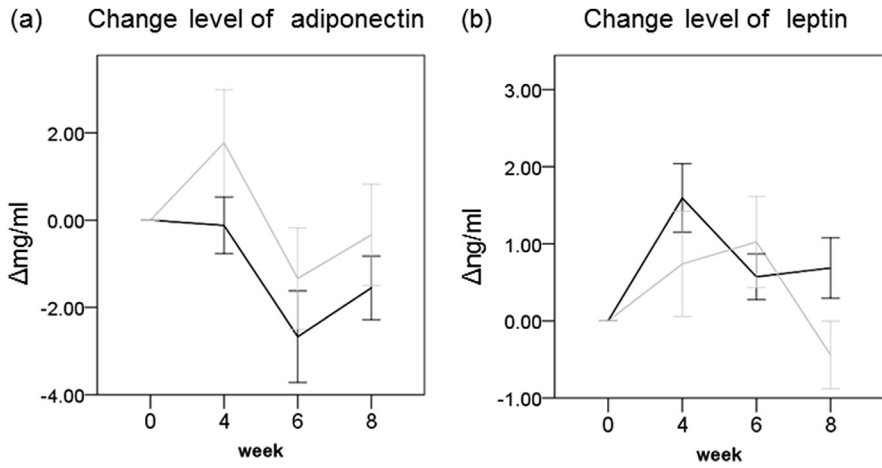
We also examined the effect of herring-roe powder on adiponectin and leptin. Although no significant between-group differences were observed in the level of serum adiponectin (Fig. 2a), leptin was slightly increased by herring-roe powder intake (Fig. 2b) (placebo:  $-0.44 \pm 1.76$  ng/ml, herring-roe:  $0.69 \pm 1.62$  ng/ml, as the change in the level of leptin from baseline to 8 weeks,  $P = 0.06$ ).

### 3.3. Levels of biomarkers of blood metabolism, liver and renal function, glucose metabolism and body composition after the ingestion of herring-roe powder

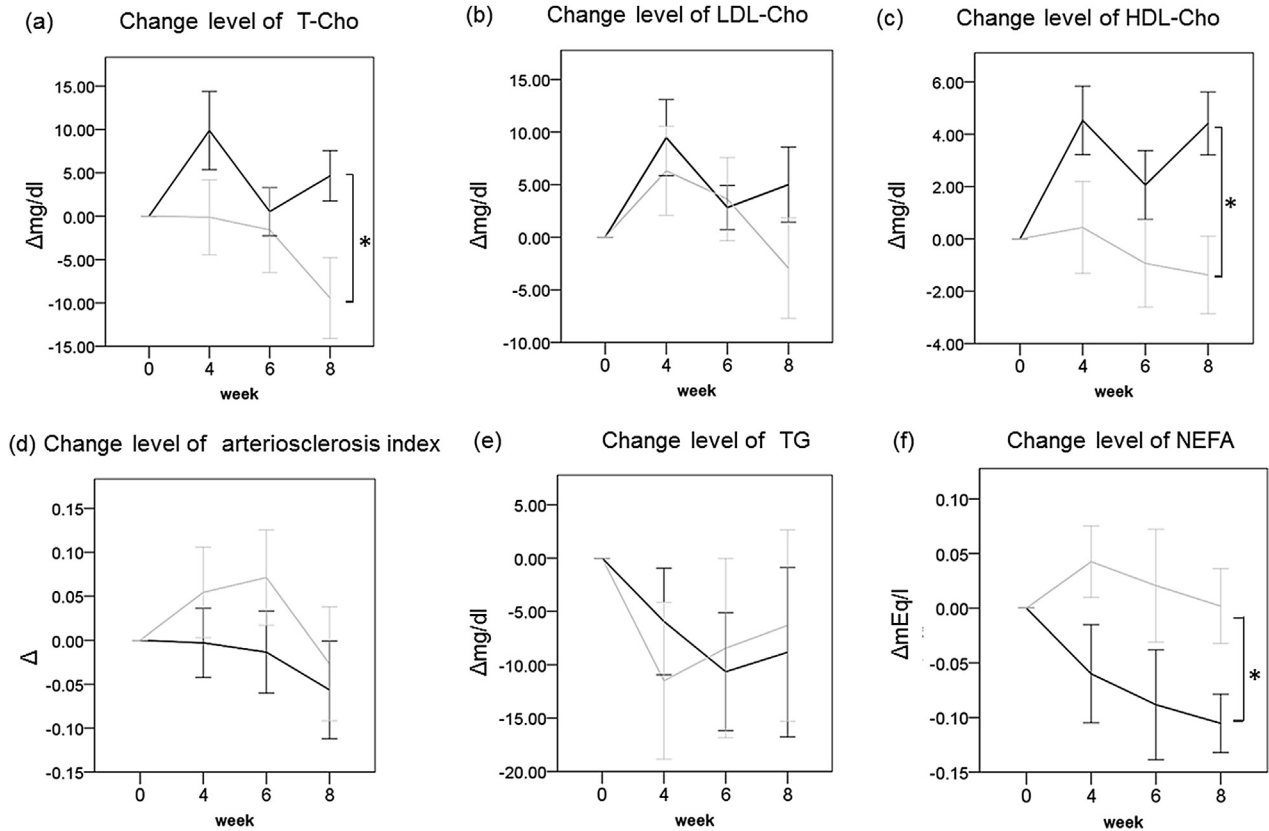
We examined the levels of several biomarkers of blood metabolism, liver and renal function, and body composition. As shown in Table 3, minimal changes were observed in the parameters of glucose metabolism [fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c)], liver function [alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and gamma glutamyl transpeptidase ( $\gamma$ -



**Fig. 1.** Time schedule (in weeks) for this clinical study. Hematological measurements were conducted at baseline (0 week), the 4th week, the 6th week, and the 8th week.



**Fig. 2.** Changes in the level of adipokine from before to after herring-roe powder intake. Values are mean ± standard error (SE). Black bar; herring-roe powder, gray bar; placebo powder. (a) Adiponectin. (b) Leptin.



**Fig. 3.** Changes in the level of lipid metabolism parameters from before to after herring-roe powder intake. Values are mean ± standard error (SE). Black bar; herring-roe powder, gray bar; placebo powder. (a) Total cholesterol (T-Cho). (b) LDL cholesterol (LDL-Cho). (c) HDL cholesterol (HDL-Cho). (d) Arteriosclerosis index (e) Triglyceride (TG). (f) Nonesterified fatty acid (NEFA).

**Table 3**  
Biochemical data.

		0 week	4 weeks	6 weeks	8 weeks
FPG (mg/dL)	Placebo	86.56 ± 9.04	86.2 ± 5.53	88.31 ± 6.15	85.19 ± 5.82
	Herring-roe	88.29 ± 10.95	89.94 ± 13.15	87.41 ± 8.82	89.35 ± 8.97
HbA1c (%)	Placebo	5.29 ± 0.26	5.3 ± 0.29	5.29 ± 0.28	5.26 ± 0.26
	Herring-roe	5.34 ± 0.33	5.38 ± 0.34	5.37 ± 0.31	5.36 ± 0.32
BW (kg)	Placebo	58.93 ± 10.34	58.48 ± 10.65	58.51 ± 10.31	58.45 ± 10.31
	Herring-roe	52.39 ± 9.74	52.34 ± 9.93	52.27 ± 10.08	52.06 ± 10.12
BMI	Placebo	23.04 ± 3.7	22.89 ± 3.81	22.83 ± 3.68	22.86 ± 3.69
	Herring-roe	20.73 ± 2.08	20.69 ± 2.16	20.66 ± 2.2	20.58 ± 2.23
Body fat rate (%)	Placebo	30.18 ± 7.57	29.72 ± 7.43	30.08 ± 7.29	30.19 ± 7.2
	Herring-roe	25.21 ± 5.42	25.62 ± 4.69	25.12 ± 4.55	25.29 ± 4.8
AST (U/l)	Placebo	22.06 ± 5.42	21.07 ± 3.54	20.94 ± 4.16	21.69 ± 5.59
	Herring-roe	21.82 ± 4.69	21.12 ± 3.66	21.12 ± 3.77	20.65 ± 3.45
ALT (U/l)	Placebo	17.88 ± 9.13	15.8 ± 5.78	16.38 ± 7.27	16.38 ± 8.32
	Herring-roe	17.53 ± 5.44	17.12 ± 5.24	17.24 ± 5.29	16.94 ± 5.06
γ-GTP (U/l)	Placebo	30.44 ± 36.17	26.2 ± 30.82	31.44 ± 42.08	33.38 ± 44.08
	Herring-roe	19.41 ± 9.13	20.00 ± 5.72	18.59 ± 4.62	19.18 ± 4.48
ALP (U/l)	Placebo	182.69 ± 61.13	180.8 ± 60.04	181.19 ± 64.85	187.56 ± 70.23
	Herring-roe	197.29 ± 48.82	194.53 ± 49.58	193.47 ± 49.15	200.53 ± 53.16
LDH (U/l)	Placebo	220.94 ± 58.13	231.33 ± 63.50	219.38 ± 52.23	233.19 ± 50.35
	Herring-roe	203.94 ± 25.80	212.00 ± 29.69	202.41 ± 17.92	208.76 ± 27.11
BUN (mg/dl)	Placebo	13.52 ± 2.60	12.97 ± 3.72	14.24 ± 2.56	13.02 ± 2.86
	Herring-roe	13.08 ± 3.72	14.31 ± 3.83	13.81 ± 3.47	14.18 ± 3.78
CRE (mg/dl)	Placebo	0.71 ± 0.09	0.71 ± 0.10	0.74 ± 0.10	0.71 ± 0.09
	Herring-roe	0.76 ± 0.14	0.73 ± 0.14	0.74 ± 0.14	0.76 ± 0.14
UA (mg/dl)	Placebo	4.84 ± 1.08	4.86 ± 1.11	4.84 ± 1.27	4.98 ± 1.46
	Herring-roe	5.04 ± 1.85	4.8 ± 2.09	4.84 ± 2.17	4.82 ± 1.94

Values are mean ± standard deviation (SD). FPG; fasting plasma glucose, HbA1c; hemoglobin A1c, BW; body weight, BMI; body mass index, ALP; alkaline phosphatase, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, γ-GTP; gamma glutamyl transpeptidase, BUN; blood urea nitrogen, CRE; creatinine, UA; uric acid.

GTP)], in the biomarkers of renal function [blood urea nitrogen (BUN), creatinine, and uric acid], and body composition [body weight (BW), BMI, and body fat rate] occurred after the ingestion of herring-roe powder, suggesting that the ingestion of herring-roe powder has no or minimal unfavorable effects on these parameters even at a dose of 15 g/day.

#### 4. Discussion

The results of our randomized, double-blind, placebo-controlled, parallel-group trial demonstrated the potential effects of herring-roe powder on lipid metabolism. The level of HDL-Cho was significantly increased and the level of NEFA was significantly decreased by the 8-week ingestion of herring-roe powder. We also observed that herring-roe powder slightly increased the level of leptin. Taken together, these results suggest that herring-roe powder improved dyslipidemia.

We observed no between-group differences in the levels of LDL-Cho. Moreover, T-Cho was decreased by ingesting the placebo powder compared to the herring-roe powder. However, HDL-Cho was increased by ingesting the herring-roe powder compared to the placebo powder. In addition, arteriosclerosis index tended to improve by ingesting herring-roe powder (herring-roe:  $-0.02 \pm 0.19$ , placebo:  $0.07 \pm 0.22$ , as the change in the level of arteriosclerosis index from baseline to 6 weeks,  $P = 0.23$ ). Low serum HDL-Cho is the risk factor of arteriosclerotic disease and seems to be more important than high serum LDL-Cho.<sup>10</sup> Herring-roe powder intake may prevent arteriosclerotic disease to improve HDL-Cho.

Moreover, herring-roe powder contained more amount of DHA than EPA (DHA 540 mg and EPA 300 mg per day). A previous study reported that DHA increased HDL-Cho and increased LDL-Cho.<sup>11</sup> These facts suggest that DHA activated lipoprotein lipase (LPL)<sup>12</sup> and facilitated degradation of TG, thereby converting very low density lipoprotein (VLDL) to LDL.<sup>13</sup> Moreover, Mori reported that

DHA induces the formation of a larger particle size of LDL.<sup>11</sup> DHA works to facilitate VLDL degradation by reduction of apolipoprotein C-III, thereby decreasing small dense LDL.<sup>14</sup> Small dense LDL has a large specific gravity and easily penetrates the vascular wall. Therefore, small dense LDL is a risk factor of dyslipidemia, arteriosclerosis, and cardiac disease.<sup>15</sup> We need to perform a subclass analysis of HDL-Cho and LDL-Cho to clarify the effects of herring-roe powder to small dense LDL in vivo or in vitro.

In addition, NEFA was decreased by test meal intake compared with placebo meal intake. NEFA secreted from enlarged adipocyte inhibits the degradation of chylomicron and very low density lipoprotein (VLDL); resulting in increased LDL-Cho. In a clinical study, ingestion of herring-roe product contained 1738 mg DHA and 616 mg EPA per day for 14 days improved NEFA and HDL-Cho, a finding that supports our present results.<sup>16</sup> In addition, NEFA inhibited glucose uptake to liver and skeletal muscle, thereby causing insulin resistance.<sup>17</sup> Herring-roe powder decreased NEFA, facilitated glucose uptake, and is thereby expected to improve blood glucose level and HbA1c. However, there were no differences in fasting blood glucose level and HbA1c between herring-roe powder and placebo powder. The reason for these results could be that the blood glucose level and HbA1c of the subjects in this clinical study were normal. We need further investigation of the effects on glucose metabolism by herring-roe powder in subjects with high blood glucose levels.

The serum leptin level was increased in herring-roe group, although the increase was not significant. Leptin is one of the peptide hormones secreted from adipocytes. Leptin inhibits appetite via the leptin receptor located in the hypothalamus.<sup>18</sup> In addition, leptin increases glucose and fatty acid consumption, thus preventing diabetes and obesity.<sup>19</sup> A previous study reported that mice fed with oil containing 5% herring-roe showed increased serum leptin levels, although the increase was not significant.<sup>20</sup> In our clinical study, herring-roe powder did not affect body weight and body fat rates, indicating that herring-roe powder did not

increase adipocyte. These results suggest that herring-roe powder increases the secretion level of leptin through adipocyte. In addition, NEFA was decreased in subjects who ingested herring-roe powder. These results suggest that the increase of leptin secretion induced the consumption of NEFA. The mechanism of the increase of leptin secretion was fully investigated; the herring-roe powder intake improved lipid metabolism via increased energy consumption and the inhibition of appetite via increased leptin secretion. Although Shirai reported that adiponectin, another adipokine, was improved by the intake of herring-roe oil,<sup>20</sup> it was not changed in our clinical study. Further investigation is required to study the effects of adipokine, leptin, and adiponectin.

## 5. Conclusion

In our clinical study, herring-roe powder did not change uric acid. Although we need to obtain more detailed data involving the mechanism of improvement of lipid metabolism, the present study suggests that the effective use of herring-roe can be beneficial for dyslipidemia without side effects.

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## Conflicts of interest

The authors state that they have no conflicts of interest to declare.

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