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Original Article

Assessment of Anti-Aging Effects of Fish Products Peptide in Middle-Aged Subjects

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Abstract

Objective: In this study, the antioxidant properties of peptide from boiled fish paste (fish products peptide; FPP) supplement were investigated in middle-aged subjects.
Methods: The subjects who participated in this study were men and premenopausal women, aged between 30 and 50 years (39.6 ± 5.5 years). The subjects consumed 10 tablets/day (containing 0.9 g of total fish peptide) for 60 days. Pre- and post-supplementation, subjects underwent analysis by physical measurement, completed the Anti-Aging QOL Common Questionnaire, and were examined in terms of vascular features, blood biochemical and uric characteristics, and hormone and oxidative stress markers.
Results: After 60 days of supplementation with FPP, significant improvement was observed in serum lipid peroxide (LPO) (–16.2 %, p = 0.001). In terms of oxidative markers, 8-hydroxy-2'-deoxyguanosine (8-OHdG) showed a tendency to decrease; in addition, potential antioxidant (PAO) and serum total antioxidant status (STAS), as antioxidant properties, showed slight increases. Furthermore, high-sensitivity C-reactive protein (hs-CRP) also exhibited a tendency to decrease.
Discussion: The results show that FPP might contribute to the prevention of lifestyle-related disease by regulating the balance of oxidative stress and improving arteriosclerosis with high oxidative stress.

KEY WORDS: Arteriosclerosis, Oxidative stress, Fish products peptide, Amino acid

Introduction

Traditionally, rice, vegetables, and fish were the main foods in Japanese cuisine, but recently the intake of other animal products has increased. Along with this change in dietary habits, the incidence of metabolic syndrome and coronary heart disease has increased [1]. In addition, interest in people's health with the progression to an aging society is growing. Public demand for healthy foods in Japan has rapidly increased. Soybean or milk peptide has become a mainstream feature of the Japanese health food market. These peptides derived from food proteins have been shown to have biological functions, such as reduction of blood pressure, ultraviolet protection of human skin, and promotion of bone formation [2-4].

Fish meat contains several ingredients that have been studied in terms of their relationship to various diseases. These include seafood-derived docosahexaenoic acid (DHA) of long-chain n-3 polyunsaturated fatty acid (n-3PUFA), which is a very stable substance. DHA reduces the risk of heart disease by reducing blood triglyceride levels, and *in vivo* reduction of DHA has been reported to cause hyperactivity disorder [5]. Moreover, administration of DHA supplement has been reported to alleviate symptoms of depression and Alzheimer's disease [6,7].

However, Japanese dietary habits include not only fish oil but also fish itself, which provides nutrients such as proteins as well as fat. It is not possible to explain from clinical data the preventive action of arteriosclerosis by piscivorous only as the function of n-3 PUFA. Therefore, there is a possibility that other actions participate in this, although there have been no reports about the function of fish-derived proteins and peptides on biological systems.

The objective of Anti-Aging Medicine is to promote health, improve QOL, and achieve healthy longevity [8,9]. The common aging parameters are divided into aging degrees and aging risk factors. The parameters of the aging degrees include muscle age, blood vessel age, neurological age, hormonal age, and bone age, while those of the aging risk factors include immune function, oxidative stress, mental and physical stress, lifestyle, and metabolism [9]. In this study, we assessed from the therapeutic perspective in Anti-Aging Medicine whether fish-derived peptide can bring about an improvement in QOL.

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Subjects and Methods

Subjects

Subjects were selected from among men and premenopausal women aged 30 to 50 years who were found to have no serious illness on physical checkup at Suzuhiro Kamaboko Honten Corporation Limited (Odawara-city, Kanagawa). Twenty volunteers (male: 10; female: 10; average age: 39.6 ± 5.5 years) who gave their written consent to participate in the test were selected as subjects.

Methods

At first, we confirmed the safety of FPP in animal experiments such as acute toxicity test and chronic toxicity test. In these studies, rats were administered FPP (10,000 mg fish peptide/kg for one week or 2,800 mg fish peptide/100g for 52 weeks); there were no deaths or abnormalities (data not shown). Therefore, in this study, subjects consumed 10 tablets/day (containing 0.9 g of total fish peptide) for 60 days. We instructed the volunteers to continue their typical lifestyle and eating habits and obtained informed consent that they would not take other antioxidant supplements during this study. The test product was provided by Fish Protein Laboratory, Research and Development Center, Suzuhiro Kamaboko Honten Corporation Limited. ***Table 1*** shows the major nutritional ingredients typically found in FPP. Toxic substances such as mercury in FPP were removed in the production processes. Each subject took a defined number of tablets one time daily after a meal. The subjects were instructed to take the study product even if they did not have a meal. When they forgot to take the study product, they were instructed as follows: If they noticed the missed dose during the same day, they were to take the missing dose immediately. Subjects were instructed to keep regular hours during this study, and maintain the same quantity and quality of sleep, diet, exercise, smoking, and alcohol intake as in their daily life prior to this study, but to refrain from alcohol one day before each inspection day.

Table 1 **Contents of FPP**

amino acid	volume(g/g)
arginine	6.44/100
lysine	9.56/100
histidine	2.13/100
phenylalanine	3.45/100
tyrosine	3.66/100
leucine	7.93/100
isoleucine	4.45/100
methionine	2.99/100
valine	4.87/100
alanine	5.62/100
glycine	3.57/100
proline	3.17/100
glutamic acid	16.40/100
serine	4.17/100
threonine	4.46/100
aspartic acid	10.20/100
tryptophan	1.07/100
cystine	0.92/100

All amino acids were analyzed by an automated amino acid analysis method with the exception of tryptophan. Tryptophan was analyzed by high-performance liquid chromatography.

This study was an open-label comparative test comparing each parameter before and after intake of the test product. This study protocol was approved by Kanagawa Dental College Research Ethics Committee, and the study was conducted in compliance with the protocol as well as the ethical principles specified in the Declaration of Helsinki and Ethical Guidelines for Clinical Research by the Ministry of Health (http://www.mhlw.go.jp/general/seido/kousei/i-kenkyu/rinri/0504sisin.html).

In accordance with the protocol, clinical assessment was performed twice, immediately before and 60 days after the start of intake of the test product. The study was conducted under the direction of Fumihiko Yoshino and Masaichi-Chang il Lee at the Clinic of Anti-Aging Medicine, Kanagawa Dental College Hospital (Yokosuka-city, Kanagawa), from February 2 to April 30, 2009.

Physical measurements and laboratory tests

Physical measurements

The following physical parameters were measured: body weight (kg), body muscle mass (kg), fat-free mass (kg), body fat percentage (%), basal metabolic rate (kcal), and BMI (measured using DC-320, Tanita Co., Itabashi-ku, Tokyo), and blood pressure (systolic/diastolic: mmHg) and pulse rate (beats/min) (measured using HEM-1010, Omron Healthcare Co., Ltd., Ukyo-ku, Kyoto).

Assessment of subjective symptoms

Subjective symptoms were divided into physical and mental symptoms and were assessed on a scale of 1 to 5 using the Anti-Aging QOL Common Questionnaire (AAQol), as reported previously [10-15]. The scores are as follows: 1: Not at all, 2: Almost none, 3: A little, 4: Moderate degree, and 5: High degree. The AAQol was downloaded from the homepage of the Japanese Society of Anti-Aging Medicine (http://www.anti-aging.gr.jp/anti/clinical.phtml).

Vascular examination

The degree of atherosclerosis was evaluated by acceleration plethysmography (Dyna Pulse SDP-100, Fukuda Denshi, Bunkyo-ku, Tokyo), and the results are expressed as vascular age [16].

Blood biochemical and uric examination

In addition to general hematology, blood biochemical tests and high-sensitivity C-reactive protein (hs-CRP) (μg/mL) were included in the test items. Hormone test items were as follows: dehydroepiandrosterone (DHEA-s) (ng/mL), homocysteine (nmol/mL), estradiol (pg/mL), total testosterone (ng/dL), insulin-like growth factor I (IGF-I) (ng/mL), adiponectin (μg/mL), and cortisol (μg/dL). 8-hydroxy-2'-deoxyguanosine (8-OHdG) (ng/kg/hr) [17,18], serum lipid peroxide (LPO) (nmol/mL), potential antioxidant (PAO) (%) [19] and serum total antioxidant status (STAS) (μM) [20] were employed as markers of oxidative stress levels. Blood testing and urinalysis were conducted by Biomarker Science Co., Ltd. (Chuo-ku, Osaka).

Statistical analysis

Statistical analysis was performed using Microsoft Excel 2002. For comparison between users and non-users of the test product, Student's *t*-test was performed with a one-sided significance level of 5 %.

Results

Variations in physical findings and physical measurements

No significant variation was observed in height, body weight, body muscle mass, fat-free mass, body fat %, basal metabolic rate, BMI, systolic and diastolic blood pressures, and pulse rate in the test period (***Table 2***).

Table 2 Physical findings and physical measurements

Item	0 day	60 days	A rate of change(%)
Age (year)	39.60 ± 5.50		
Height (cm)	165.75 ± 7.42	165.71 ± 7.32	−0.02
Body weight (kg)	63.33 ± 12.76	63.35 ± 12.20	0.04
Body muscle mass (kg)	43.23 ± 9.00	43.78 ± 8.74	1.61
Fat-free mass (%)	45.70 ± 9.42	46.29 ± 9.13	1.28
Body fat % (%)	27.72 ± 6.00	26.83 ± 5.70	−3.19
Basal metabolic rate (kcal)	1308.65 ± 237.97	1323.20 ± 229.57	1.11
BMI (kg/m^2)	22.92 ± 3.59	22.96 ± 3.42	0.2
Systolic BP (mmHg)	127.30 ± 19.83	120.50 ± 16.00	−5.34
Diastric BP (mmHg)	80.25 ± 16.03	75.75 ± 13.53	−5.61
Pulse rate (beats/min)	69.25 ± 12.77	63.70 ± 13.78	-8.01

Subjects: n = 20. Measured values: average ± standard deviation.

Changes in subjective symptoms and lifestyle shown by Anti-Aging QOL Common Questionnaire

As shown in ***Table 3***, of 32 physical parameters in AAQol, no significant variation was observed. Improvement involving a decrease of over 10 % was observed in three parameters, skin problems (–11.1 %, p = 0.14), early satiety (–10.6 %, p = 0.18), and tinnitus (–11.6 %, p = 0.21). Of 21 mental symptoms, no symptom significantly improved with FPP intake (***Table 4***). Improvement involving a decrease of over 10 % was observed in six parameters, easily angered (–10.5 %, p = 0.18), daily life is not enjoyable (–18.2 %, p = 0.08), depressed (–15.2 %, p = 0.12), feeling useless (–13.3 %, p = 0.15), inability to solve problems (–15.1 %, p = 0.08), and inability to sleep due to worries (–17.0 %, p = 0.07).

Vascular examination

In accelerated plethysmography, vascular age tended to decrease from 46.75 ± 13.23 to 40.55 ± 12.23 years (–13.3 %, p = 0.066) with FPP intake (***Table 5***).

Variations in values obtained in blood biochemistry and uric examination

The blood biochemistry and uric examination results of before and after the supplementation were compared. In the blood biochemistry, no significant variation was observed regarding LDL cholesterol (–1.3 %, p = 0.44), HDL cholesterol (–1.6 %, p = 0.35), and triglyceride (0.6 %, p = 0.42) (***Table 6***). In CRP, a tendency to decrease was observed, but a significant difference was not recognized (***Table 6***). In hormone test, no significant change was observed in DHEA-s, homocysteine, total testosterone, adiponectin, cortisol, and DHEA-s/cortisol ratio (***Table 7***). Estradiol tended to increase from 71.05 ± 85.9 to 92.6 ± 137.3 pg/mL (30.8 %, p = 0.27). IGF-I tended to decrease

Table 3 AAQol (physical symptoms)

Item	0 day	60 days	A rate of change(%)
Tired eyes	2.75 ± 1.16	2.85 ± 1.14	3.64
Blurred vision	2.15 ± 1.09	2.25 ± 0.91	4.65
Painful eyes	1.65 ± 0.81	1.75 ± 0.91	6.06
Stiff shoulders	3.65 ± 1.04	3.60 ± 1.05	−1.37
Muscular pain/stiffness	3.40 ± 1.05	3.15 ± 1.09	−7.35
Palpitations	1.90 ± 0.91	1.85 ± 0.99	−2.63
Shortness of breath	1.90 ± 1.02	1.95 ± 1.00	2.63
Tendency to gain weight	3.15 ± 1.04	3.20 ± 0.89	1.59
Weight loss/thin	1.70 ± 0.86	1.95 ± 0.83	14.71
Lethargy	2.90 ± 0.91	2.65 ± 0.88	−8.62
No sense of wellness	2.32 ± 0.88	2.45 ± 1.10	4.26
Thirst	2.25 ± 1.02	2.25 ± 1.02	0
Skin problems	3.15 ± 1.09	2.80 ± 0.89	−11.11
Anorexia	1.75 ± 0.85	1.75 ± 0.72	0
Early satiety	2.35 ± 0.93	2.10 ± 0.79	−10.64
Eplgastralgia	2.00 ± 0.86	2.05 ± 0.94	2.50
Liable to catch colds	2.40 ± 0.82	2.30 ± 0.86	−4.17
Coughing and sputum	2.30 ± 0.98	2.10 ± 0.85	−8.70
Diarrhea	2.05 ± 0.89	2.10 ± 0.85	2.44
Constipation	2.70 ± 1.49	2.80 ± 1.32	3.70
Hair loss	2.30 ± 0.92	2.10 ± 0.72	−8.70
Gray hair	2.80 ± 1.06	2.65 ± 1.04	−5.36
Headache	2.50 ± 1.05	2.45 ± 1.05	−2.00
Dizziness	2.20 ± 1.11	2.10 ± 1.02	−4.55
Tinnitus	2.15 ± 1.09	1.90 ± 0.79	−11.63
Lumbago	3.30 ± 1.03	3.10 ± 1.12	−6.06
Arthralgia	2.10 ± 1.12	2.25 ± 1.02	7.14
Edematous	2.85 ± 1.09	2.70 ± 0.98	−5.26
Sweat easily	2.65 ± 1.09	2.75 ± 1.02	3.77
Frequent urination	2.45 ± 1.15	2.65 ± 0.93	8.16
Hot flashes	1.95 ± 0.76	1.85 ± 0.88	5.13
Cold skin	3.25 ± 0.76	3.00 ± 1.26	−7.69

Subjects: n = 20. Measured values: average ± standard deviation.

Table 4 AAQol (mental symptoms)

Item	0 day	60 days	A rate of change(%)
Irritability	2.80 ± 1.06	2.55 ± 0.89	−0.89
Easile angered	2.85 ± 1.09	2.55 ± 0.94	−10.53
Lost of motivation	2.45 ± 0.94	2.35 ± 1.04	−4.08
Unhappy	2.25 ± 0.79	2.10 ± 0.85	−6.67
Nothing to look forward to in life	2.05 ± 0.89	1.95 ± 1.05	−4.88
Daily life in not enjoyable	2.20 ± 0.95	1.80 ± 0.77	−18.18
No confidence	2.55 ± 0.94	2.30 ± 0.92	2.63
Reluctance to talk with others	2.15 ± 0.75	2.10 ± 0.79	−2.33
Depressed	2.30 ± 0.98	1.95 ± 0.89	−15.22
Feeling useless	2.25 ± 0.97	1.95 ± 0.83	−13.33
Shallow sleep	2.05 ± 0.69	1.95 ± 0.83	−4.88
Difficulty in falling asleep	1.80 ± 0.77	2.00 ± 0.92	11.11
Pessimism	2.70 ± 1.03	2.45 ± 1.00	−9.26
Memory lapse	3.20 ± 0.89	3.00 ± 1.03	−6.25
Inability to concentrate	2.55 ± 0.60	2.40 ± 0.94	−5.88
Inability to solve problems	2.65 ± 0.93	2.25 ± 0.79	−15.09
Inability to readily make iudgments	2.60 ± 0.68	2.60 ± 0.82	0
Inability to sleep due to worries	2.35 ± 0.81	1.95 ± 0.83	−17.02
Feeling tense	2.85 ± 0.75	2.60 ± 0.75	−8.77
Feeling anxious for no paticular reson	1.95 ± 0.83	1.90 ± 0.79	−2.56
Vague feeling of fear	1.90 ± 0.72	1.90 ± 0.97	0

Subjects: n = 20. Measured values: average ± standard deviation.

Table 5 Vascular examination

Item	0 day	60 days	A rate of change(%)
vascular age	46.75 ± 13.23	40.55 ± 12.23	−13.26

Subjects: n = 20. Measured values: average ± standard deviation.

Table 6 Blood biochemical and uric examination

Item	0 day	60 days	A rate of change(%)
LDL-cholesterol (mg/dL)	143.85 ± 55.27	141.10 ± 54.51	−1.34
HDL-cholesterol (mg/dL)	71.60 ± 17.16	141.10 ± 54.51	−1.64
Triglycerides (mg/dL)	101.10 ± 70.34	96.50 ± 66.18	0.16
Fe (μg/mL)	94.90 ± 38.16	89.95 ± 43.45	−5.22
Fasting glucose (mg/dL)	109.20 ± 44.63	104.55 ± 44.63	−3.12
hs-CRP (μg/dL)	103.05 ± 212.72	57.05 ± 63.02	−44.64
Uric acid (mg/dL)	5.28 ± 1.70	5.23 ± 1.59	−0.85

Subjects: n = 20. Measured values: average ± standard deviation.

Table 7 Hormone and oxidative stress markers

Item	0 day	60 days	A rate of change(%)
DHEA-s (ng/mL)	1666.50 ± 699.87	1537.95 ± 720.02	−7.71
Homocystein (nmol/mL)	8.07 ± 2.05	8.66 ± 2.36	7.31
Estradiol (pg/mL)	71.05 ± 85.99	92.95 ± 137.31	30.82
Total testosterone (ng/dL)	249.40 ± 253.16	255.50 ± 249.89	2.45
IGF-I (ng/mL)	232.80 ± 79.48	209.25 ± 65.36	−10.12
Adiponectin (μg/mL)	9.85 ± 4.13	9.50 ± 4.45	−4.00
Cortisol (μg/mL)	9.05 ± 4.05	8.25 ± 2.97	−2.01
DHEA-s / Cortisol	20.86 ± 10.03	20.74 ± 11.86	−1.00
Serum LPO (nmol/mL)	3.60 ± 0.76	2.94 ± 0.50	−18.36 *
8-OHdG (ng/kg/hr)	6.29 ± 4.33	5.64 ± 2.94	−10.41
PAO (%)	1055.15 ± 216.33	1066.60 ± 213.56	1.09
STATS (μM)	1195.90 ± 119.08	1232.15 ± 124.10	3.03

Subjects: n = 20. Measured values: average ± standard deviation
* $p < 0.001$ Comparison with before intake of FPP (0 day) (unpaired t-test).

from 232.8 ± 79.5 to 209.3 ± 65.4 ng/mL (–10.1 %, $p = 0.16$). 8-OHdG as an oxidative-stress marker showed a tendency to decrease (–10.4 %, $p = 0.29$). Additionally, serum LPO showed a significant decrease (–16.2 %, $p = 0.001$) (***Table 7***). PAO (1.0 %, $p = 0.43$) and STATS (3.0 %, $p = 0.18$) as antioxidant properties showed slight increases (***Table 7***).

Safety

With regard to the safety of this product, no other adverse effect was observed in the subjects before and after the supplementation of FPP.

Discussion

Fish is known to be good for health. In particular, it has been reported that DHA contained in fish lipid decreases the cholesterol secretion from the liver to the plasma because it inhibits the generation of cholesterol [21]. In addition, DHA suppresses the synthesis of the fatty acid of the related enzyme. It is known that DHA is effective for prevention and improvement of cerebrovascular disorders, dementia, ischemic heart disease, high blood pressure, arteriosclerosis, chronic inflammation, hyperlipidemia, and dermatitis by decreasing arachidonic acid in plasma and internal organs [22-25]. The beneficial effects to health and amelioration of cardiovascular and cerebrovascular diseases due to fish are caused by a combination of the suppressing effect on blood coagulation of n-3 PUFA and the promoting effect on fibrinolysis of fish protein [26]. However, it has been reported that DHA supplementation increased oxidative damage in bone marrow DNA [27]. On the other hand, fish protein has been reported to decrease cholesterol, which influences the lipid metabolism of human subjects in serum and liver [28].

In this present study, hs-CRP [29], which is known as a factor related to arteriosclerosis, showed a tendency to decrease (***Table 6***). Moreover, serum LPO decrease and antioxidant property (PAO and STATS) increase were recognized as other factors in arteriosclerosis (***Table 7***). It has been reported that the sequence of Phe-Gly-Ala-Ser-Thr-Arg-Gly-Ala of fish peptide inhibits angiotensin I converting enzyme (ACE) [30], and ACE inhibitor is effective against arteriosclerosis [31]. Therefore, this phenomenon shows the possibility that ACE inhibition of FPP improves the inflammatory condition of blood vessels throughout the body.

Secondarily, it is possible that FPP intake may contribute to the improvement and prevention of circulation disease by its antioxidant properties. FPP is composed of several kinds of amino acids (***Table 1***). It is possible that FPP is broken down to amino acids in the intestinal tract, which are distributed to the whole body after absorption by the intestinal tube wall. It has been reported that several proteins, peptides, and amino acids have the antioxidant property to reactive oxygen species (ROS) [32]. As for arteriosclerosis, its relationship with oxidant stress influenced by ROS, such as superoxide ($O_2^{\bullet -}$) and hydroxyl radical ($HO^{\bullet}$), is well known [33,34]. Therefore, it is suggested that FPP was absorbed as amino acids, and the amino acids inhibited lipid peroxidation by antioxidant properties, and serum LPO decreased as a result. In particular, these amino acids are considered to be a leading part of the antioxidant property so that tyrosine included in FPP may scavenge $O_2^{\bullet -}$ [35] and phenylalanine, histidine, and tryptophan may scavenge $HO^{\bullet}$ [35]. Furthermore, FPP showed tendencies for increased PAO and STATS in addition to a decrease of serum LPO. Therefore, FPP may be a supplement with antioxidant properties and/or capacity to accelerate the antioxidant activity in biological systems. It is suggested that the intake of FPP decreased the vascular age as a result of integrating this ACE inhibition and antioxidant properties. It is necessary to examine the mechanism of action of fish peptide including FPP in detail so that the oxidant stress may be involved in various diseases [36].

In conclusion, we examined the effect of Anti-Aging Medicine by FPP intake. The Anti-Aging effect was found to involve inhibition of oxidative stress pathways involved in vascular diseases such as arteriosclerosis. Therefore, continuous intake of FPP might contribute to the prevention of lifestyle-related diseases by regulating the balance of oxidative stress; however, further studies are needed for elucidation of the mechanisms underlying the relationship between FPP and vascular effects, including the influence of ACE.

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