

HEALTH AND NUTRITION NEWS

No. 18

December 15, 2006



Table of Contents

PREFATORY NOTE

Future perspectives of nutritional sciences as an academic field.....**Yukiko Miura**

CURRENT RESEARCH PROJECTS

Project for Shokuiku.....**Naomi Aiba**

THOUGHTS ON HEALTH AND NUTRITION RESEARCH

Dietary survey should reflect the regional characteristics **Akemi Morita**

RESEARCH FINDINGS

Resistance training and arterial compliance: keeping the benefits while minimizing the stiffening
..... **Motohiko Miyachi**

Moisture and mineral content of human feces -- high fecal moisture is associated with increase sodium
and decreased potassium content --**Mamoru Nishimuta**

Dietary folate intakes and folate biomarker profiles of pregnant Japanese women
.....**Natsuko Mito, Keizo Umegaki, Nobuo Yoshiike**

Docosahexaenoic acid-induced lipid peroxidation and urinary excretion of mercapturic acid
.....**Morio Saito**

Prefatory Note

Future perspectives of nutritional sciences as an academic field

Yukiko Miura
Senior researcher,
National Institute of Science and Technology Policy
Ministry of Education, Culture, Sports, Science and Technology



The third Science and Technology Basic Plan (2006-2010) was formulated in the spring of 2006. This plan indicates the direction of Japan that proclaims to establish a nation based on the creativity of science and technology in the national strategy. The following three principles are stated in the chapter of principles and policy goals; 1) to develop the wisdom of human, 2) to create the sources of national strength, 3) to protect health and safety of the people. The first two principles may bring the distant image of science and technology, as the general public would have, whereas the last one clearly shows for whom science and technology are used.

Well, the nutrition science is the academic field from which everyone can equally enjoy and acknowledge its research outcome. It is therefore important to obtain the accurate information and understand its message correctly. Let me bring an example here; we can use a mobile phone without knowing its mechanism, while it could be dangerous to take a dietary supplement without knowing its effect properly.

In reality, however, while we are now surrounded by an overflow of information, we hardly know how to evaluate its reliability. To make the matter worse, in many cases, we are not aware of our lack of knowledge. Some people may realize that they wrongly used the health foods, only after the serious health hazard caused by these health foods are reported in the media.

The National Institute of Health and Nutrition (NIHN) has the website of “Information system on safety and effectiveness for health foods (<http://hfnet.nih.go.jp>: in Japanese only)”, and the hit count is currently about five millions. I expect that the NIHN will continue to enhance the functions of this website, and also that more people will utilize it.

In Japan, many people tend to be allergic to the term of “science and technology”, assuming that it must be incomprehensible. Besides, there are the scientists who do not take it important to facilitate the general public to understand science and technology. Yet, I would request the people who work on the health science to face fully with these problems. As the staff at the Ministry of Education, Culture, Sports, Science and Technology, one of our duties is to raise awareness of importance that “The sciences should be understood correctly by everyone” among both the public and the scientists.

I am grateful to the experts who work for our health promotion in the research and clinical field, and now, I would expect them to advocate, through their practices, the importance of explaining to the people based on scientific evidences as well as making them understand correctly to the scientists in other academic fields. This is why I put the above title to this prefatory note.

** The original Japanese version was translated by Project for International Research and Development, NIHN*

Summary of The third Science and Technology Basic Plan (2006-2010)

• Basic principles •

▶ Basic stances

- 1) Science and technology that are supported by society and people and return the outcomes to society
 - to improve the levels of science constantly ⇨ creation of intellectual and cultural values
 - to return the research outcomes to society and people through innovation ⇨ creation of social and economic values
- 2) emphasis on human resource development and competitive environment for research

▶ Clarification of policy goals in science and technology

In order to clarify the targets of the government research and development investment, the following concrete policy goals are set under the three basic principles;

- (1) breakthrough of significant knowledge (2) breaking the limitation of science and technology
- (3) simultaneous pursuit of environmental preservation and economic development
- (4) contribution of Japan as an innovator (5) healthy living throughout one's life
- (6) the country that can be proud of secure public security

▶ Government research and development investment

Total amount is about 25 trillion yen (1% of GDP during the 5 year plan, with 3.1 % GDP nominal growth rate)

Current Research Projects

Project for Shokuiku

Naomi Aiba
Project for Shokuiku

Recently, the opportunities to see and hear of the term of “Shokuiku” have been gradually increasing. The Basic Law on Shokuiku was enacted in 2005, followed by formulation of the Basic Plan for Promotion of Shokuiku in March 2006. The main targets set in this Basic Plan are shown in **Table 1**.

The Basic Law on Shokuiku was enacted due that various social problems had been occurring, including change of food environment (social and natural environment) and increase of various diseases associated with unbalanced diet (e.g. lifestyle-related diseases). Shokuiku is therefore promoted as a national movement with the aims that Japanese people will have healthy livings both physically and mentally throughout ones’ lives and also that an environment to foster rich humanity will be established.

Project for Shokuiku works on the researches under the slogan of “Health Promotion throughout our lives”, so as to explore the appropriate approaches (when, how) to draw attention of people on diet and to change one’s dietary behaviors. Besides, the environmental settings necessary to implement these approaches are also investigated.

The numerical targets of reducing breakfast skippers and increasing awareness on metabolic syndrome set in the Basic Plan for Promotion of Shokuiku eventually aim to reduce the people at risk of metabolic syndrome, especially by changing one’s dietary behaviors. For which, in addition to dissemination of the relevant information, nutrition



The first national convention on Shokuiku promotion (June, 2006)

education should be designed in the way that each individual can achieve behavioral change.

In particular, food education for children should not be enough if it is implemented only within the educational curriculum at school, as it is crucial to involve their families/communities too continuously. In order to eliminate breakfast skipping, it is essential to review the lifestyle resulting in breakfast skipping, instead of simply encouraging children to take breakfast. We therefore propose a practical nutrition education program where the food education can be implemented effectively, with providing scientific evidences to work out how each individual can improve one’s lifestyle, and how school and family can support it.

In addition, we also propose an education program on “Shokuiku” by incorporating it in the integrated study class at school.

Table 1. Numerical targets in the Basic Plan for Promotion of Shokuiku

Targets	Baseline (2006)	by 2010	
Having an interest in Shokuiku	70%	90%	
Skipping breakfast	(elementary school)	4%	0%
	(20-29 years old)	30%	≤ 15 %
	(30-39 years old)	23%	≤ 15%
Use of local agricultural products in school lunch menu	21%	≥ 30%	
Use of the Food Balance Guide, as a guide to pursue appropriate diet	-	≥ 60%	
Awareness on metabolic syndrome	-	≥ 80%	
Number of volunteers working on Shokuiku promotion	-	≥ +20%	
Municipalities with education farm	42%	60%	
Having basic knowledge on food safety	-	≥ 60%	
Prefectures planning/implementing the Basic Plan for Promotion of Shokuiku	-	100%	
Municipalities planning/implementing the Basic Plan for Promotion of Shokuiku	-	≥ 50%	

Thoughts on Health and Nutrition Research

Dietary survey should reflect the regional characteristics

Akemi Morita

Project for lifestyle-related diseases prevention

I have visited various areas in Japan, even not all over the country, for the purpose of surveys and researches, where there are many occasions to hear dialect and term specific to the area from the local people. At a survey in Okinawa undertaken in the early summer, when I asked the municipality staff to check the greeting letter for the expected participants, they corrected the term used in the seasonal greeting from the standard “*shoka* (= early summer)” to Okinawa dialect “*urizun*”. In Okinawa, “*urizun*” is used as a term to express the specific season (around February-March of lunar calendar) when animals and plants grow well, and the field soil becomes fertile. I was really impressed to hear this beautiful term that reflects the regional characteristics very well. Next, when I went to a rural village in the northern part of Japan (*Tohoku* district), I asked the municipality staff whether there was an area-specific seasonal term. Then, they mentioned “season of *sanaburi*” which is used to express June. “*Sanaburi*” is the traditional festivity held after a period of rice planting, in order to celebrate the god of paddy field. While “*sanaburi*” is very old practice, people in some areas still continue to hold this festivity.

Not surprisingly, the area-specific terms can be observed at the dietary survey too. For example, when we call “*soba*”, it generally means the one made of buckwheat. However, when people in Okinawa say “*soba*”, this mean “*Okinawa soba*” made of wheat. Likewise, the food composition of *tofu* (*shima tofu*) in Okinawa is very different from the standard hard *tofu*. In addition, the weight of one unit of *tofu* is also different (300-350g in Tokyo vs. 1kg in Okinawa). Recently, some of *soba* or *tofu* shops expand the service to all over Japan, by utilizing the internet, and thus, there is a possibility that the answer of “*soba*” or “*tofu*” in Okinawa may be the standard ones and vice versa.

Vegetable names could also vary by region; for example, pumpkin is “*kabocya*” in the standard Japanese, while it is called differently in some areas like “*nanban uri*”, “*boubura*”, “*nankin*”, “*tounatsu*” etc. Likewise, for kidney beans and corn, it is generally called in the standard Japanese as “*ingen mame*” and “*toumorokoshi*” respectively. On the other hand, in the Kansai area where I was grown up, we called

them “*sando mame*” and “*nanba*”, respectively. When I was in the childhood, I always called the deep-fried tofu mixed with thinly sliced vegetables as “*hirousu*”. Thus, when I heard of “*ganmodoki*” on TV, I was wondering what it was like, while in fact they were the same food. When it comes to dishes, I guess that there are more terms that I used in Kansai, but people in other areas would not understand; for example, boiled egg (“*ninuki*” in Kansai vs. “*yudetamago*” in Tokyo), boiled eel with rice (“*mamushi*” in Kansai vs. “*unadon*” in Tokyo)

It is said that the current young generations tend to use the standard Japanese, rather than local dialect. Yet, when I conducted the interviews for junior high school students to obtain the data on their dietary intake, one of them said “*daikon no taitan*” which is the Kansai dialect meaning “*daikon no nimono* (= boiled radish)”. Since the interviewer was the dietitian from outside Kansai, she looked perplexed to understand what it meant. Well, I was happy to interpret for her, feeling pleasant to see that the Kansai dialect still commonly used by the local junior high school students.

Needless to say, the preliminary research should be undertaken to obtain the relevant information including the local foods and dishes, and based on which the questionnaires and detail implementation plan should be established. In addition, whenever I carry out a survey, I would emphasize the importance of local dialect related to diet and local dishes by working in collaboration with the local dietitians and people living in the study area.



Latest Research

Resistance training and arterial compliance: keeping the benefits while minimizing the stiffening.

Motohiko Miyachi (Health Promotion and Exercise Program)

Reduction in central arterial compliance, as represented by carotid arterial compliance, is an independent risk factor of cardiovascular diseases. It has been well known that regular aerobic training increases carotid arterial compliance. In contrast, we have recently demonstrated that high-intensity resistance training is associated with reduced carotid arterial compliance. Yet, since resistance training contributes to the prevention of sarcopenia and significantly reduces the risk of being in need of nursing care, it has become an integral component of exercise guidelines endorsed by a number of national health organizations. It is therefore meaningful to investigate the type of resistance training that does not induce the reduction in arterial compliance.

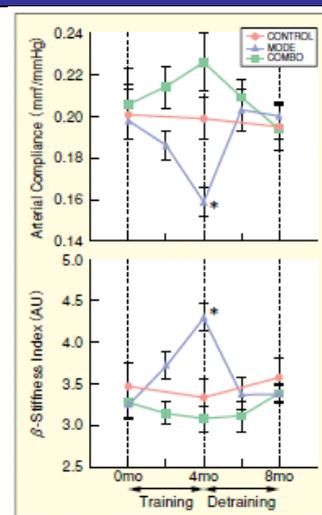
In this context, two strategies appear plausible; one is moderate exercise training and the other is the combined training where regular aerobic exercise and high-intensity resistance training are performed simultaneously. Accordingly, the primary aim of the present study was to longitudinally examine the effects of moderate-intensity resistance training as well as the combined strength and endurance training on carotid arterial compliance.

A total of 39 young healthy men were studied. Subjects were randomly assigned into three groups; 1) the moderate intensity resistance training group (MODE), 2) the combined high-intensity resistance training and moderate-intensity aerobic exercise training group (COMBO), 3) sedentary control group (CONTROL). In the first four months of study period (exercise intervention period), participants in all training groups underwent three supervised resistance training sessions per week. During each training session, participants in the COMBO group completed three sets of 10 exercises at 80% of 1RM and subjects in the MODE group completed three sets of 16 exercises at 50% of 1 RM in the following order: leg extension, seated chest press, leg curls, lateral row, squat and sit-ups. In addition, subjects in the COMBO group performed a cycle exercise at 60% of the maximal heart rate for 30 min immediately after each resistance training session. Following the exercise intervention period, detraining was implemented for a period of four months, in order to confirm that the observed changes in arterial compliance were induced by the prescribed exercise training.

Carotid arterial compliance decreased after four months of MODE interventions ($p < 0.05$), whereas arterial compliance did not decrease, but rather tended to increase ($p = 0.06$), after 4 months of the COMBO intervention (Figure). After the detraining period, arterial compliance values returned to the baseline level in both groups. No significant changes in carotid arterial compliance were observed in the CONTROL group throughout the eight months' study period. Furthermore, peripheral (femoral) artery compliance did not change in any groups.

In the present study, we demonstrated that simultaneously performed endurance training prevented the reduction in arterial compliance that was accompanied by high-intensity resistance training. One possibility is that the profound effects of regular aerobic exercise (e.g improved endothelial function, shared stress) may have negated the opposing effects of resistance training.

It is therefore important to recommend that aerobic training should be performed simultaneously with resistant training, when the exercise guidance is provided for prevention of nursing care and lifestyle-related diseases.



Resistance training and arterial compliance: keeping the benefits while minimizing the stiffening.

Journal of Hypertension. 2006; 24(9): 1753-59.

Kawano H^{1),2),3)}, Tanaka H⁴⁾, Miyachi M¹⁾

1) Division of Health Promotion and Exercise, National Institute of Health and Nutrition, Tokyo, Japan

2) Graduate School of Human Sciences, Waseda University, Saitama, Japan

3) Department of Health and Sports Sciences, Kawasaki University of Medical Welfare, Okayama, Japan

4) Department of Kinesiology and Health Education, University of Texas, Austin, Texas, USA

Abstract: **OBJECTIVES:** This study aimed to determine the effects of moderate resistance training as well as the combined resistance and aerobic training intervention on carotid arterial compliance. **BACKGROUND:** Resistance training has become a popular mode of exercise, but intense weight training is shown to stiffen carotid arteries. **METHODS:** Thirty-nine young healthy men were assigned either to the moderate-intensity resistance training (MODE), the combined resistance training and endurance training (COMBO) or the sedentary control (CONTROL) groups. Participants in the training groups underwent three training sessions per week for 4 months followed by four additional months of detraining. **RESULTS:** All training groups increased maximal strength in all the muscle groups tested ($P < 0.05$). Carotid arterial compliance (via simultaneous carotid ultrasound and applanation tonometry) decreased approximately 20% after MODE training (from 0.20 ± 0.01 to 0.16 ± 0.01 mm²/mmHg, $P < 0.01$). No significant changes in carotid arterial compliance were observed in the COMBO (0.20 ± 0.01 to 0.23 ± 0.01 mm²/mmHg) and CONTROL (0.20 ± 0.01 to 0.20 ± 0.01 mm²/mmHg) groups. Following the detraining period, carotid arterial compliance returned to the baseline level. Peripheral (femoral) artery compliance did not change in any groups. **CONCLUSIONS:** We concluded that simultaneously performed aerobic exercise training could prevent the stiffening of carotid arteries caused by resistance training in young healthy men.

Latest Research

Moisture and mineral content of human feces -- high fecal moisture is associated with increase sodium and decreased potassium content --

Mamoru Nishimuta (Nutritional Epidemiology Program)

The origin of moisture in diarrhea feces is unknown, but may come from the unabsorbed part of dermal contents or body fluids excreted into the digestive canal. If body fluids do contribute to the moisture content of feces, it is possible that active transport of water (H₂O) associated with ion exchange channels may be involved in this process. In order to investigate this possibility, we measured moisture and mineral content (sodium [Na], potassium [K], calcium [Ca], magnesium [Mg], phosphorus [P], zinc [Zn], iron [Fe], copper [Cu], manganese [Mn]) in feces during a 12-d metabolic study on 11 young Japanese female students.

The study was carried out as part of a human mineral balance study. The same quantity of food was supplied to each of the subjects throughout the study without consideration of body weight. Fecal specimens were collected throughout the study and were separated into those originating from the diet during the balance period (12 d) based on the appearance of the ingested colored marker in the feces.

The relationship between moisture and the Na and K content are shown in **Figure 1**. The moisture content of the feces ranged between 53 and 92%. Na content in the feces was low and stable when the moisture content was below 80%, whereas it increased up to serum levels when the moisture content increased above 80%. In contrast, K content increased when compared to dry matter base, with concentration/g moisture increasing when moisture was below 70% and decreasing when moisture was above 70%. Accordingly, in the moisture range above 80%, there was a negative correlation between fecal Na and K content (**Figure 2**).

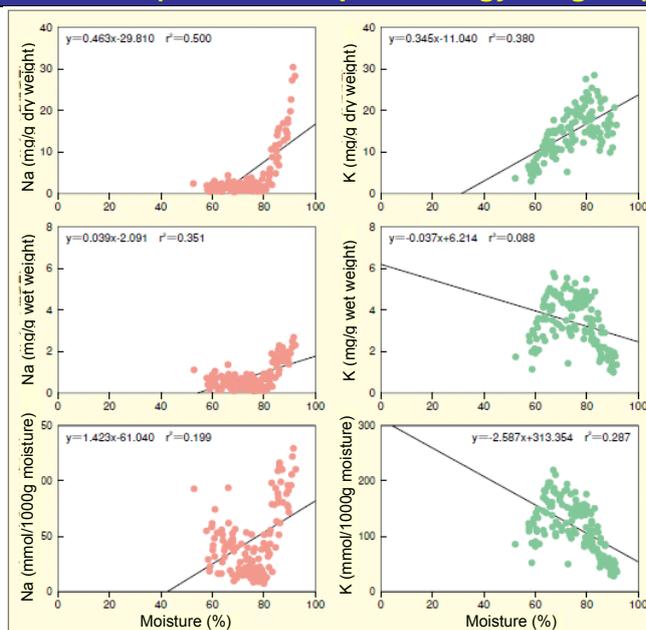


Fig 1. Relationships between moisture and Na and K contents in feces

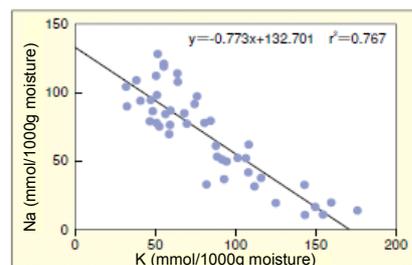


Fig 2. Relationships between concentrations of fecal Na and K (fecal moisture > 80%)

Moisture and mineral content of human feces -- high fecal moisture is associated with increase sodium and decreased potassium content --

Journal of Nutritional Science and Vitaminology. 2006; 52: 121-126.

Nishimuta M¹⁾, Inoue N¹⁾, Kodama N¹⁾, Morikuni E^{1),2)}, Yoshioka YH¹⁾, Matsuzaki N¹⁾, Shimada M^{1),3)}, Sato N^{1),4)}, Iwamoto T^{1),5)}, Ohki K^{1),6)}, Takeyama H^{1),7)}, Nishimuta H⁸⁾.

1) Laboratory of Mineral Nutrition, Division of Human Nutrition, National Institute of Health and Nutrition, Tokyo, Japan

2) Medical University of Yamanashi, Yamanashi, Japan

3) Chiba College of Health Science, Chiba, Japan

4) Seitoku University, Chiba, Japan

5) Prefectural University of Hiroshima, Hiroshima, Japan

6) Showa Women's University, Tokyo, Japan

7) Nagoya City University Graduate School of Medical Science, Nagoya, Japan

8) Third Department of Surgery, Toho University Ohashi Hospital, Tokyo, Japan

Abstract: **BACKGROUND:** The origin of moisture in diarrhea feces is unknown but may represent the unabsorbed part of intestinal contents or alternatively, body fluid excreted into the digestive canal. If the latter mechanism contributes to moisture in the feces, active transport of water (H₂O) associated with ion exchange channels may be involved. **OBJECTIVE:** To investigate this possibility we measured the content of moisture and minerals (sodium [Na], potassium [K], calcium [Ca], magnesium [Mg], phosphorus [P], zinc [Zn], iron [Fe], copper [Cu] and manganese [Mn]) in feces collected during a 12-d metabolic study on 11 young Japanese female students. **DESIGN:** The study was carried out as part of a human mineral balance study. The same quantity of food was supplied to each of the subjects throughout the study without consideration of body weight. Fecal specimens were collected throughout the study and were separated into those originating from the diet during the balance period based on the appearance of the ingested colored marker in the feces. **RESULTS:** The moisture content of the feces ranged between 53 and 92%. Na content in the feces was low and stable when the moisture content was below 80%, whereas it increased up to serum levels when the moisture content increased above 80%. On the other hand, K content increased when compared to dry matter base. However, when comparing concentration/g moisture, K content increased when moisture was below 70%, but decreased when this rose above 70%.

Latest Research

Dietary folate intakes and folate biomarker profiles of pregnant Japanese women.

Natsuko Mito (Food Function and Labeling Program), Keizo Umegaki (Information Center), Nobuo Yoshiike (Center for Collaboration and Partnership)

Folate is a water-soluble vitamin B, which is involved in DNA synthesis relevant to cell proliferation. Recent studies have shown that an adequate intake of folic acid significantly reduces the risk of neural tube defects (NTDs). NTD is a congenital abnormality that occurs in the neural tubes such as brain and spinal cord of babies. Since the neural tubes are formed in early pregnancy, the periconceptional use of folic acid is very important for primary prevention of NTD. Leaf vegetables, fruits, beans and liver are rich sources of folate. The bioavailability of dietary folate is not so high, and some people may not be able to take sufficient folate from diet only. The Ministry of Health Labour, and Welfare (MHLW), Japan recommends that all women planning a pregnancy should consume an additional 400 μ g/day of folate from supplemental folic acid.

So far, many studies on dietary folate intake and serum folate concentration have been undertaken in Western countries, but there is no sufficient data on Japanese. Accordingly, we conducted this study to investigate the association between dietary folate intake and serum folate concentrations of Japanese women in early pregnancy.

A total of 70 healthy pregnant women in the first trimester were included in this study. Weighted dietary records were obtained from each subject for three nonconsecutive days within a week, from which the mean daily consumption of nutrients and foods was estimated. In addition, fasting blood samples were drawn for the measurement of hematological parameters (hemoglobin, hematocrit, RBC count) and folate-related biomarkers.

Mean folate intake in all subjects was 289 μ g/day in the present study, which is lower than the recommended dietary allowance (RDA) of folate in early pregnancy (440 μ g), according to the Dietary References Intakes for Japanese 2005. On the other hand, the mean serum folate concentration was remarkably higher than the one reported in other countries. When we analyzed the consumption of nutrients and foods in the two groups defined by serum folate concentration, the intakes of calcium, fiber, spinach and fruits were significantly greater in the high folate (serum folate \geq 9ng/ml) group than in the low folate group. Serum folate levels were positively correlated with other blood markers (plasma vitamin B₁₂, albumin, hematocrit)

It is known that the bioavailability of folate varies widely with different foods and cooking style, and our findings suggest that the eating pattern in Japanese may have a unique factor, by which serum folate concentration can be maintained high.

It is reported that insufficient folate intake may increase the risk of not only NTD, but also atherosclerosis and cardiac diseases. Further study is needed on other age groups of Japanese as well.

This study was undertaken with the research grant by the MHLW Japan (Principal investigator: Nobuo Yoshiike).

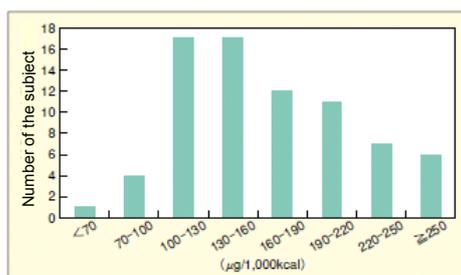


Figure 1. Distribution of dietary folate intake

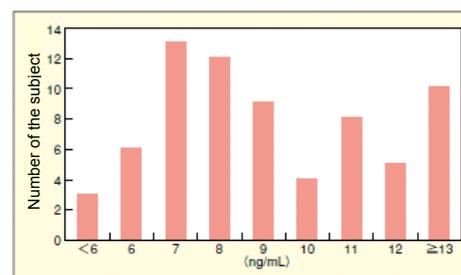


Figure 2. Distribution of serum folate concentration

Folate intakes and folate biomarker profiles of pregnant Japanese women in the first trimester.

European Journal of Clinical Nutrition. 2007; 61:83-90

Mito N¹⁾, Takimoto H²⁾, Umegaki K¹⁾, Ishiwaki A³⁾, Kusama K⁴⁾, Fukuoka H⁵⁾, Ohta S⁶⁾, Abe S⁷⁾, Yamawaki M⁸⁾, Ishida H⁹⁾, Yoshiike N³⁾.

1) Division of Applied Food Research, National Institute of Health and Nutrition, Tokyo, Japan

2) Section of Maternal and Child Health, Dept. of Health Promotion and Research, National Institute of Public Health, Japan

3) Division of Health and Nutrition Monitoring, National Institute of Health and Nutrition, Tokyo, Japan

4) Dept. of Health Science, Faculty of Human Life and Environmental Science, Kochi Women's University, Kochi, Japan

5) Dept. of Developmental Medical Science, Graduate School of International Health, University of Tokyo, Tokyo, Japan

6) Obstetrics and Gynecology Unit, Ohta Hospital, Tokyo, Japan

7) Dept. of Obstetrics and Gynecology, Metropolitan Otsuka Hospital, Tokyo, Japan

8) Matsushima Women's and Children's Hospital, Tokyo, Japan

9) Laboratory of Administrative Dietetics, Kagawa Nutrition University, Saitama, Japan

Abstract: **Objective:** To assess the status of dietary folate intake, serum and red blood cell (RBC) folate, and related nutritional biomarkers in healthy Japanese women in early pregnancy. **Design:** A cross-sectional, observational study. **Subjects:** Pregnant women in the first trimester, at 7-15 weeks gestation (n=70), who were not consuming any folate supplements or folate fortified foods. **Methods:** Three-day dietary records were obtained from each subject to assess dietary folate intake. Blood samples were collected for measurement of biomarkers. Biomarkers and nutrient intake were analyzed in two groups defined by their serum folate concentrations: the low folate group (serum folate < 9 ng/ml) and the high folate group (serum folate \geq 9 ng/ml). **Result:** Mean serum and RBC folate concentrations in all subjects were 10.3 and 519 ng/ml, respectively. These levels were remarkably higher than the reported values from many other countries despite our subjects receiving no folic acids supplements. However, mean folate intake by our subjects from natural foods was 289 μ g/day, which is thought to be low according to the Japanese dietary recommendation specified for pregnant women. The intake of spinach and fruits was significantly greater in the high folate group than in the low folate group. **Conclusion:** Folate intake was thought to be adequate to maintain a desirable level of serum folate concentration in Japanese pregnant women in the first trimester, although the intake of folate from natural food was not high enough to meet the recommended daily intake. **Sponsorship:** This study was funded by a Ministry of Health Labour and Welfare, Health and Labour Research Grant, for Research on Children and Families.

Docosahexaenoic acid-induced lipid peroxidation and urinary excretion of mercapturic acid.

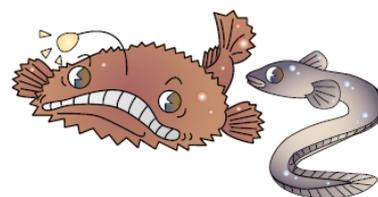
Morio Saito (Food Function and Labeling Program)

The preventive effects of n-3 polyunsaturated fatty acid (PUFA) on cardiovascular diseases are well acknowledged. In particular, docosahexaenoic acid (DHA) is the predominant n-3 PUFA with distinctive physiological functions. Recently, the relationship between DHA and anti-inflammatory action in inhibitory effects on atherosclerosis becomes a hot issue. However, n-3 PUFAs are very prone to lipid peroxidation because of its unstable chemical structure, and thus there is a concern that a high level of DHA intake would enhance the susceptibility to in vivo lipid peroxidation. Focusing on the most highly unsaturated DHA, we have undertaken the animal studies using rats as a model animal, with a hypothesis that "There are primarily two suppressive mechanisms against PUFA-induced lipid peroxidation in healthy body; one is an antioxidative mechanism that suppresses generation of lipid peroxides, and the other is a detoxification and/or excretion mechanism". It was, then, found that tissue lipid peroxides increased in a DHA dose-dependent manner, though it reached a plateau and did not increase to the extent as calculated by Peroxidizability index (a parameter that indicates the maximal rate of peroxidation). In addition, even with a very high dose of DHA, neither the end products of lipid peroxidation (e.g. lipofuscin) nor tissue damages were observed. We therefore confirmed that the above hypothesis was feasible and thus further investigations have been carried out.

So far, we have revealed and published the following antioxidative mechanisms; 1) the uptake of DHA is different by tissues and the unsaturation level of membrane fatty acids is important to produce lipid peroxides, 2) the uptake of DHA in phospholipid species is different by tissues, and the resistance to oxidation increases when DHA is ingested into phosphatidylethanolamine, 3) a very high level of DHA intake transiently increases the uptake of DHA in tissue triglyceride, by which DHA can be protected from oxidation, 4) induction of antioxidative enzymes is not observed, 5) the increased generation of ascorbic acid (AsA) and glutathione (GSH) induced by DHA intake, which also increases the antioxidative potency of Vit. E, 6) it is impossible to suppress lipid peroxidation completely even with a high-dose of Vit. E, AsA and GSH. Yet, since no adverse effect has been initiated, we have investigated the mechanisms of suppressing accumulation and detoxification and/or excretion of lipid peroxides. Of which, a part of the findings is reported in this paper.

We have previously observed that lipid peroxidation-derived degradation products, particularly reactive aldehydic compounds, did not form the Schiff base by reacting with macromolecules, hence the end products of lipid peroxidation (lipofuscin) were not detected. In this study, therefore, we hypothesized that detoxification and/or excretion mechanisms of aldehydic compounds would occur in the course of formation of the end products of lipid peroxidation. Then, our findings showed a possible pathway as follows; the aldehydic compounds induced after a high level of DHA intake would form conjugates with GSH in the liver, which is transferred to the kidney through the blood stream, metabolized and converted to the mercapturic acid, and eventually excreted into urine⁽¹⁾. We also explored for the first time that the excretion process of the conjugates in the liver may be mediated by MRP3 (ABCC3), one of the ABC transporter families⁽²⁾. Besides, aldose reductase and aldehyde dehydrogenase may be involved in the metabolism of the aldehydic compounds⁽¹⁾. Further studies are underway.

It is very important to reveal the dynamics of PUFA-induced lipid peroxidation for their effective utilization. We believe that our findings demonstrated some ingenious detoxification and/or excretion mechanisms.



<Reference>

- (1) Sekine S, Kubo K, Tadokoro T, Saito M. Docosahexaenoic acid-induced lipid peroxidation and urinary excretion of mercapturic acid in rats. *J Clin Biochem Nutr* 2006; 39: 40 - 45.
- (2) Kubo K, Sekine S, Saito M. Induction of multidrug resistance-associated protein MRP3 in liver of rats fed docosahexaenoic acid. *Biosci Biotech Biochem* 2006; 70: 1672 - 1680.

Docosahexaenoic acid-induced lipid peroxidation and urinary excretion of mercapturic acid in rats

Journal of Clinical Biochemistry and Nutrition. 2006; 39: 40-45

Sekine S^{1,2)}, Kubo K^{1,3)}, Tadokoro T²⁾, Saito M¹⁾,

1) Division of Food Science, National Institute of Health and Nutrition, Tokyo, Japan

2) Laboratory of Nourishment Biochemistry, Dept. of Applied Biology and Chemistry, Tokyo University of Agriculture, Tokyo, Japan

3) Nursing Course, Narabunka Women's College, Incorporated Educational Institution, Nara Gakuen, Nara, Japan

Abstract: We hypothesized a suppressive mechanism for dietary docosahexaenoic acid (DHA)-induced tissue lipid peroxidation in which the degradation products, especially aldehydic compounds, are conjugated with glutathione (GSH) through catalysis by glutathione S-transferases (GSTs), and then excreted into urine as mercapturic acids. Sprague-Dawley rats were fed a diet containing DHA (8.4 % of total energy) for 31 days. Lipid peroxides in the liver and kidney, liver GST and urinary excretion of mercapturic acid were measured. The lipid peroxide levels in the liver and kidney except the liver aldehydic compounds were higher, and the urinary excretion of mercapturic acid also tended to be higher in the DHA-fed rats although the activity of GST was not increased after DHA intake. We presume from our results that a proportion of the lipid peroxidation-derived aldehydic degradation products might be excreted into urine as mercapturic acid after intake of DHA, thus suppressing the accumulation of aldehydic products in tissues, particularly in the liver.