

HEALTH AND NUTRITION NEWS

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Prefatory Note

Interviews with the new Director-General



Shaw WATANABE
Director-General, NIHN

As a new Director-General...

Ministry of Health, labor and welfare has declared to enhance the control of lifestyle-related diseases. This time, I accepted to take up the present position, and am honored to be the Director-General of the research institute with an 85-years history. I myself have diabetic mellitus, and have been controlling over the disease well through diet and exercise. Through my experiences, I'm now well aware that diet and exercise are essential for the healthy living. Generally, people in good health are not conscious of being "healthy", and rather tend to consider "health maintenance" and "health promotion" as the issue of other people. I hope that our Institute will accumulate the scientific knowledge necessary for good health, following the "Health Frontier Plan".

Role of our Institute

Since it is not a big institute, I would aim at a research institute as think tank open to the public. The annual National Nutrition Survey which started after the World War II is a great asset. "Nutrition" can be largely divided into two; "preventive nutrition" for health promotion, and "clinical nutrition" in the hospital. So, I would attempt to organize the team that could work on both types of nutrition, for which the registered dietitians may play important roles. Besides, it is also important to clarify the basic mechanism by animal experiments and in-vitro ones, as these finding could eventually be applied to human beings. In Japan, we used to suffer from the serious food shortage in the past, while we are now surrounded by the excessive foods. In addition, various nutritional supplements are now widely used seeking for better health. However, an intervention has explored that excess intake of β -carotene has rather negative impacts on human's health. Consequently, the importance of human study is now well recognized.

About the supplement use

Since there is no post marketing surveillance (PMS) for the supplements, I would like to establish it systematically. For which, a cohort study by the Nutrition Representative (NR) and registered dietitians in cooperation with the food industries could bring practical and great impacts.

In Japan, there is a traditional terms from oriental medicine regarding diet for health (e.g. "*shokuyou* (=Taking foods in a healthy way for better health)", "*ishoku dogen* (=Medicine and one's daily diet are equally important in making a sick body well)"), and I would like to establish the scientific evidence for these terms. So, I shall work on the management of NIHN in collaboration with various organizations. Since it concerns "food", at the governmental level, it is important to establish the collaboration not only with the Ministry of Health, Labor and Welfare, but also with the Ministry of Agriculture, Forestry and Fisheries. The understanding of Ministry of Education, Culture, Sports, Science and Technology is also inevitable for the implementation of "*shokuiku* (=Promotion of learning on the healthy diet from an early stage, in particular on the choice of foods, to secure the healthy living over the course of one's life). Likewise, a project for which all the ministries work together may be needed in the field of health science. Since information based on the evidence is highly required, I would enhance the function as an information center at our Institute.

Foods for specified health use

"Therapeutic diets" and "Foods specified for health use" may sound similar, but there is a significant difference between them. The former has been utilized for patients in many hospitals, whereas the latter has insufficient evidence regarding the effects for human bodies. I think, therefore, the standard should

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be revised sooner or later. Since there has been no systematic evaluation for the application to be qualified as the “Foods specified for health use”, more strict design will be required in the human studies

Regarding the nutrition labeling, the responsibility should be basically put on the consumers themselves as well as the food companies, by which only the products with appropriate label will survive in the market. However, the labeling of biological and pharmacological functions is practically difficult with respect to the Pharmaceutical Affairs Law. Besides, the descriptions of these functions would contain the technical terms, most of which are difficult for the consumers to understand. Yet, the FAO/WHO Codex Alimentarius Commission now recommends the labeling of these functions as well, if it really works on the disease preventions.

About the use of various supplements

Few supplements have the label on the maximum limit of intake. So, some people may believe that more intakes should be better. It must be noted, however, that the excess intake of even so-called “healthy food” may cause rather negative impacts on health.

The interaction between foods and medicine has been gradually known. Likewise, the combined intake of food and supplements should also be carefully considered.

We, human beings, would take foods following the experiences of thousands' years, while we are not yet certain about the consequence of the long-termed intake of supplements. It is therefore not advisable to rely on the supplements only without taking the

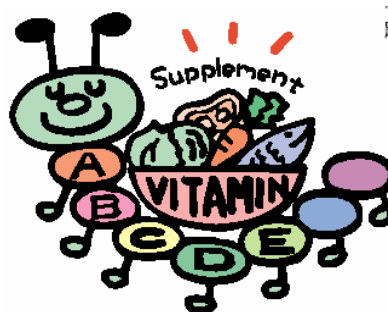
ordinal diets, for which NR could play an important role.

Recommendations for the food industry

Human bodies require lipid, protein and carbohydrate, which are consumed more than one ton annually. With a rapid increase of diabetic mellitus and obesity in Japan, it is very important for us to know the actual energy intake. Therefore, I would like to request the food companies to put more easily understandable nutrition labeling on each food products.

For example, for most of the food products, energy is shown in the unit of “per 100g”, but what we actually would like to know is energy per packet/serving. In addition, the present standard for labeling allows that less than five kcal can be shown as “0 kcal”, but I suggest it should be more realistic to show it as “< 5 kcal”. Although food companies tend to fully follow the ministerial decrees on the standardized labeling, showing the accurate energy could earn more trust from the consumers. Development of low-calorie foods is also very important in order to control the obesity among the populations.

From interviews for “Food Industry Newspaper”



Profiles

Graduated from Keio University School of Medicine in 1965. Majored in pathology in the graduate school, after which he worked for National Cancer Institute (USA) and National Cancer Center (Japan). In 1985, he was appointed as the chief of Division of Epidemiology, where he explored the new field of cancer etiology and molecular epidemiology. From 1996, he worked on a new research on “Environment, food, health” at Tokyo University of Agriculture. He is one of the world authorities in the field of functional food factors. He is also the Director of Association for promotion of life science. Awarded WHO memorial medal in 1993, Medical Award of the Japan Medical Association in 1995, and a merit medal from the Japanese Epidemiological Association. He has been in the present position since 2005.

Current Research Projects

Laboratory of Biological Function of Food Components

Yoshiko Ishimi

Division of Applied Food Research

Laboratory of Biological Function of Food Components is mainly in charge of the evaluation of function and health effects of food components related to bone metabolism and lipid metabolism, as well as the analyses of “Foods for Special Dietary Use”.

Although bone may look a calm organ, in reality, active metabolism takes place. Bone functions not only as a supporting organ for the whole body, but also as storage of calcium (Ca). Since Ca is the most important mineral to maintain one's life, in response to the shortage of Ca content in the blood, metabolic control works to stabilize blood Ca level by eluting Ca from bone. Therefore, bone is important organ not only to support the body, but also for the vital activity.

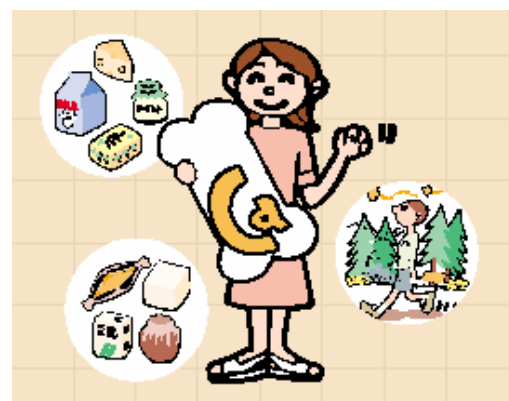
Determinants of bone mass include genetic factors, nutrition, exercise, life style and hormone. In particular, deficient secretion of estrogen after menopause could bring a serious consequence, that is, a rapid progress of bone loss. Unless one stores a sufficient bone mass during the youth, bone density will be low due to the menopause and she will be prone to breaking bones, namely “postmenopausal osteoporosis”. It is estimated that about half of Japanese women would experience the bone fracture due to postmenopausal osteoporosis.

Osteoporosis is called as a silent disease, as it is asymptomatic at the initial stage. Once one gets bone fracture, however, there is a high possibility that she will be bedridden for her remained life. Consequently, QOL of the elderly will be greatly affected. Recently, Ministry of Health, Labour and Welfare implements various policies to reduce the number of elderly persons who require the long-termed nursing care, of which we would emphasize that the prevention of bone fracture should be most important problem.

Under this circumstance, we have been working on the researches with the aim to establish the preventive methods of osteoporosis, which could be practiced effectively in the daily life. Focusing on the compounds derived from Soya that has a weak estrogenic activity, we have been investigating the effects of soya intake on

the abnormal bone/lipid metabolism observed after the menopause. In addition, an experimental study for animal as well as for human is also implemented, in order to examine if the combination of soya diet and exercise could increase the effects. In the human study, we instruct the volunteers after menopause to continue the quick walking 3 times per week and daily soybean isoflavone intake, and then, we keep monitoring the impact on the bone/lipid metabolism. If the preventive effects of diets and exercise are confirmed from this experiment, elderly people will be able to enjoy more healthy life, and thus the medical expenses will be reduced.

Nowadays, with various health foods available in the market and overflowing information, we may find it difficult to decide how and which foods to choose. Since 2001, the National Institute of Health and Nutrition has been working on the evaluation of the effects of ingredients in the so-called health foods which have not been scientifically proved, focusing on the health effects and safety against the lifestyle related diseases. Of which, our Laboratory is responsible for the evaluation on the food components of health foods that advertise the effects for maintaining the health of bone and cartilage. Our latest research findings are updated regularly in the website of our Institute (in Japanese only). Please refer to the following website for the background information of the above project; http://www.nih.go.jp/eiken/english/researchz/juuten_shokuhin_e.html



Thoughts on Health and Nutrition Research

Connexin genes have wide range of tumor-suppressive effects

Tomohiro Yano
Division of Applied Food Research

Tumor cells are greatly heterogeneous with various characters, which is one of the main factors to make the cancer prevention and treatment complicated. Antitumor drug does not take effect all the times, and some of the carcinoma tissues have the antitumor drug resistance. Cancer recurrence, invasion and metastasis are attributable to these resistant tissues, which makes it difficult to recover completely. Control of the survival and growth of these malignant tumor cells is therefore very important. Generally, the grade of malignancy is defined by the level of dedifferentiation from the highly differentiated normal cells. In order to control the survival and growth of the malignant tumor cells effectively, it is important to recover and maintain the functions of gene cluster necessary for the differentiation of normal cells. Among these gene clusters, we focused on Connexin genes, which express the gap junction. Connexin genes maintain the intercellular homeostasis by equalizing intracellular concentration of hydrophilic molecule ($M_w \leq 1300$) among adjacent cells, by which the differentiation of cells can be preserved. We, therefore, attempted to establish the procedures for cancer prevention and treatment by utilizing the tumor-suppressive effects of Connexin genes.

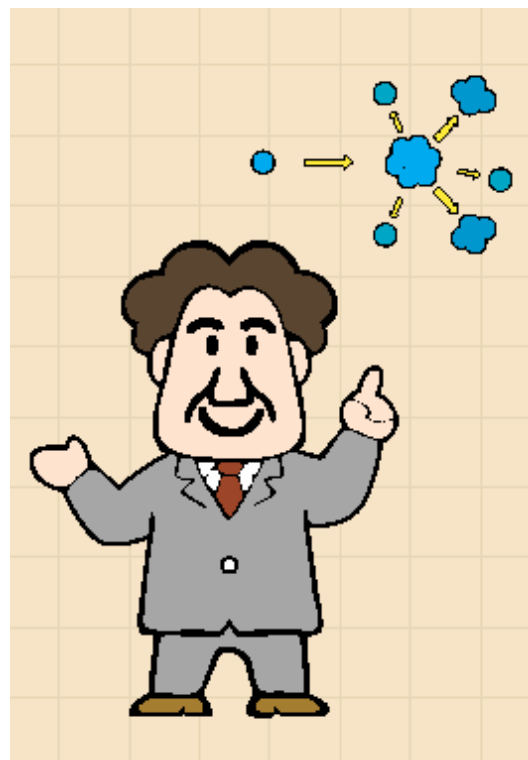
Fortunately, I was given an opportunity to work at Unit of Multistage Carcinogenesis, the International Agency for Research on Cancer (IARC) in Lyon of France for 20 months from October 1998. IARC is a part of WHO, and was a leading center at that time for the analyses of tumor-suppressive effects of Connexin genes. I was able to acquire in-depth knowledge on various tumor-suppressive effects of Connexin genes, by which I could further develop the subsequent researches.

Initially, Connexin genes were known mainly by the expression of gap junction which could suppress the growth of cancer cell. Later, it was further explored that Connexin genes widely contribute to maintain the differentiation of normal

cells, by controlling the cell attachment and cytoskeletal formation independently of gap junction, and also as an essential gene for expression and maintenance of protein necessary for the normal cell functions.

Furthermore, recent studies showed that Connexin genes could control comprehensively the signal system related to invasion and metastasis, by which invasion and metastasis can be inhibited even in metastatic malignant tumor cells. This finding would suggest that tumor-suppressive effects of Connexin genes could widely contribute to the cancer prevention and treatment.

In the future, further attempts will be made to establish the procedures for cancer prevention and treatment by targeting the recovery of effects of Connexin genes that work differently by the type of cancer. I hope that our research team could make a significant contribution in this study theme.



Effects of tube-fed liquid formula with dietary fiber in the bed-ridden elderly patients

Takashi Kumae (Division of Health Promotion and Exercise)

A liquid diet fed through a nasogastric tube is used for patients who cannot take a meal orally and is more physiologic than intravenous feeding. A liquid diet has the added advantage of being adaptable for home patients because it does not require the same high levels of sterility that are associated with intravenous feeding. A liquid diet is the most nutritionally appropriate for elderly patients bedridden for a long term.

Dietary fiber (DF) may be presented in two forms; one is water-insoluble fiber and the other is water-soluble one. These components have different physiologic and nutritional effects. Digestion in the small intestine is affected mainly by water-soluble DF, whereas the regulation of large intestine functions and fecal excretion are associated mainly with water-insoluble DF. The purpose of a DF-containing liquid diet include a decrease or elimination of diarrhea, which is the most common complication, and an increase of stool volume to maintain an appropriate environment in the large intestine. Oligosaccharides, which are resistant to digestion and absorption in human small intestine, has recently received attention as a prebiotic or DF.

In this study, a liquid diet containing two kinds of DF (water-insoluble cellulose and water-soluble oligosaccharide) was administered to twenty-two elderly bedridden patients (9 men and 13 women) for 4 weeks. The effects were monitored by changes in blood parameters and bowel movement. No patients reported problems associated with blockage of the nasogastric tube due to DF administration.

Although DF is known to inhibit the absorption of nutrients, in this study, body weight of both male and female increased slightly during the first 15 days of the trial. Besides, there was no change in nutritional parameters such as total protein, hemoglobin, albumin, total cholesterol, triacylglycerol, HDL cholesterol, calcium, iron and magnesium during the administration of liquid diets. These findings would suggest the beneficial effects of a liquid diet with cellulose and oligosaccharides. It must be noted, however, that this was a short-termed controlled study, and that a more detailed analysis are required to clarify not only the health effects, but also the possible side effects of DF and oligosaccharides.

A tube-fed liquid formula diet containing dietary fiber increased stool weight in bed-ridden elderly patients.

Nutrition. 2004 Nov-Dec;20(11-12):955-60.

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Abstract:

OBJECTIVE: The number of bedridden elderly patients who need a liquid diet has been increasing. We evaluated the usefulness of a tube-fed liquid diet containing cellulose and oligosaccharide for elderly bedridden patients. **METHODS:** Twenty-two elderly bedridden patients were given a liquid diet containing cellulose and labinose for 4 wk. Parameters associated with blood and stool weight were measured during this period. **RESULTS:** Stool weight increased by 32.0 g in men and 8.8 g in women at 2 wk and remained at these weights up to 4 wk ($P < 0.05$ before and after 2 wk, 3 wk, and 4 wk in men, and $P < 0.05$ before and after 3 wk in women). Body weight increased in men (0.5 kg) and women (0.7 kg) 15 d after starting the diet and then remained at these values up to 29 d thereafter, and statistically significant differences were not seen. There were no changes in nutritional parameters such as total protein. **CONCLUSION:** No significant changes were observed in the general condition of elderly patients, with the exception of a positive increase in fecal weight, by 30-d supplementation of a liquid diet containing cellulose and labinose.

Suppressive effect of *Citrus Aurantium* against body fat accumulation and its safety.

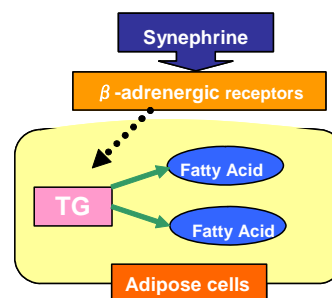
Kazuhiro Kubo (Division of Food Science)

In Japan, *Citrus aurantium* (CA) is known as a kind of orange (*dai-dai*), which has been used for a specific ornament on the New Year's Day and also for herbal medicine. *Citrus*, an old name of lemon tree, means a kind of oranges, and *Aurantium* means orange-yellow in Latin. CA is also called as "sour orange" or "bitter orange". CA is now popularly used as an ingredient of many ephedra-free supplements for dieting. The active constituent of CA is considered to be synephrine, and its suppressive effect against body fat accumulation is thought to occur through β -adrenergic receptors. Receptors, located on/inside cell membrane, change the cell functions in response to the external factors (e.g. hormone, light). Likewise, adrenergic receptors become activated by the binding of adrenaline or noradrenalin.

There are two types of adrenergic receptors; one is α -receptor that basically brings excitatory effects and the other is β -receptor that brings suppressive effects. These receptors further can be divided into α_1 , α_2 , β_1 , β_2 and β_3 , each of which has various effects. .

Studies on the associations between β -adrenergic receptors and lipolysis have been reported mostly by examining the white adipose cells of mammals. Of which, it is also explored that β_3 -adrenergic receptor strongly promotes lipolysis and thermogenesis. Synephrine, which is an active constituent of CA, is said to stimulate and activate β_3 -adrenergic receptor. Because of its suppressive effect against body fat accumulation, Synephrine is used in many diet products.

One study reported that in humans a suppressive effect against body fat accumulation occurs when synephrine-containing CA is taken with other stimulants such as caffeine, but no other human study has been done regarding the effect of synephrine on body fat accumulation. In this study, therefore, we focused on the suppressive effects of synephrine-containing CA against body fat accumulation and its safety in rats.



Suppressive effect of *Citrus Aurantium* against body fat accumulation and its safety.

Journal of Clinical Biochemistry and Nutrition. 2005;36:11-17.

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Division of Food Science, National Institute of Health and Nutrition, Japan

Abstract:

A large number of so-called diet foods containing *Citrus aurantium* (CA) and its active constituent, synephrine, for suppressing body fat accumulation are currently on the market. However, only one human study has demonstrated the efficacy of CA, and its potential cardiotoxicity has been reported in a rat study. Therefore, we investigated the safety of CA and its suppressive effect against body fat accumulation in rats. High fat (20% (w/w)) diets containing CA (synephrine content, 6.4%) at 0, 40, 200, 1000 and 5000mg/kg diet were fed to rats *ad libitum* for 79 days. For dieting, the recommended daily intake of CA in many dietary supplements ranges from 100 to 1000mg/day, and the amount used in this experiment was approximately equivalent to 40 and/or 200mg/kg diet. In the 5000mg/kg CA group, the adrenaline and dopamine concentrations in plasma were significantly higher, perirenal fat pad weight was significantly lower, and body weight tended to be lower than in the control group. Although no abnormalities of serum clinical and biochemical parameters were observed except for adrenaline and dopamine, and also no histopathological abnormalities were evident in the heart, heart weight in the 5000mg/kg CA group was significantly lower than in the control group. Therefore, it is necessary to examine more precisely the potential cardiotoxicity caused by excess intake of CA. Particularly, the elucidation of influences of the simultaneous intake of CA and some stimulants, such as caffeine, awaits further characterization.

Activities of DGAT in the liver, with respect to intra-abdominal obesity and steatosis

Tomomi Yamazaki (Division of Clinical Nutrition)

In the liver, Triglyceride (TG) is synthesized and its excessive accumulation could lead to steatosis. The synthesized TG is either stored in cytoplasmic droplets or secreted as very low density lipoprotein (VLDL) particles. Acyl-CoA:diacylglycerol acyltransferases (DGATs) is a membrane-bound enzyme that catalyzes the last step in triglyceride (TG) synthesis. Classified by detergent sensitivity, two types of DGATs in microsomes have been proposed: the overt type (on the cytosol) catalyzes the synthesis of TG destined for cytoplasmic droplets, and latent type (on the lumen of endoplasmic reticulum (ER)) catalyzes the synthesis of TG for VLDL formation.

There are two types of DGAT enzyme; DGAT1 and DGAT2, which are unrelated proteins that exhibit DGAT activity. In order to elucidate the roles of DGAT1 and DGAT2 in the liver, especially in the overt and latent DGAT activities, we created liver DGAT1- and DGAT2-overexpressing mice by adenovirus-mediated gene transfection, and then their phenotypes were investigated.

DGAT1-overexpressing mice had increased latent DGAT activity and a dilated ER, whereas these changes were not observed in DGAT2-overexpressing mice. As expected from the increased latent

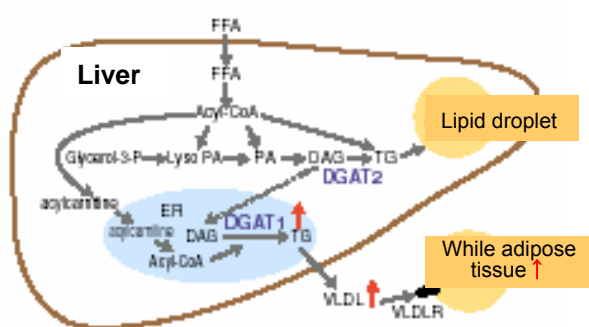


Figure. Activities of DGAT1 and DGAT2, and increased fat mass

DGAT activity in DGAT1-overexpressing mice, VLDL secretion and particle size were increased, resulting in increased gonadal fat mass expressing a large amount of VLDLR. This finding highlights the importance of the VLDLR in the etiology of some types of obesity, that is, intra-abdominal obesity.

In conclusion, our findings suggest that it would be possible to prevent obesity and steatosis by suppressing the activity of DGAT1 and DGAT2 respectively. It is therefore recommended to establish dietary management to control the activities of DGAT so as to maintain good health.

Increased very low density lipoprotein secretion and gonadal fat mass in mice overexpressing liver DGAT1.

Journal of Biomedical Chemistry, 2005 Jun 3;280(22):21506-14

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Abstract: Acyl-CoA:diacylglycerol acyltransferases (DGATs) catalyze the last step in triglyceride (TG) synthesis. The genes for two DGAT enzymes, DGAT1 and DGAT2, have been identified. To examine the roles of liver DGAT1 and DGAT2 in TG synthesis and very low density lipoprotein (VLDL) secretion, liver DGAT1- and DGAT2-overexpressing mice were created by adenovirus-mediated gene transfection. DGAT1-overexpressing mice had markedly increased DGAT activity in the presence of the permeabilizing agent alamethicin. This suggests that DGAT1 possesses latent DGAT activity on the lumen of the endoplasmic reticulum. DGAT1-overexpressing mice showed increased VLDL secretion, resulting in increased gonadal (epididymal or parametrial) fat mass but not subcutaneous fat mass. The VLDL-mediated increase in gonadal fat mass might be due to the 4-fold greater expression of the VLDL receptor protein in gonadal fat than in subcutaneous fat. DGAT2-overexpressing mice had increased liver TG content, but VLDL secretion was not affected. These results indicate that DGAT1 but not DGAT2 has a role in VLDL synthesis and that increased plasma VLDL concentrations may promote obesity, whereas increased DGAT2 activity has a role in steatosis.