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Prefatory Note

Lifestyle –related diseases and the National Institute of Health and Nutrition

Dr. Kuzuya Nobuaki
Director of Clinical Laboratory,
Department of Endocrinology and Metabolism, International Medical Center of Japan

Lifestyle–related disease is defined as “syndromes related to one’s lifestyle such as diet, physical exercise, rest, smoking and drinking with its onset and development”. The population of lifestyle-related diseases such as diabetes, high blood pressure, hyperlipidemia, and obesity has significantly increased in recent days. Each disease above can be a risk factor for developing arteriosclerosis. Also, a patient may be affected with more than one lifestyle-related disease. Blindness due to diabetic retinopathy and patients under hemodialysis by diabetic renopathy both increased Cerebral infarction and ischemic heart disease, which are arteriosclerotic ivents, increased in the elderly. This increase in lifestyle-related diseases not only occupies the leading causes of death in Japan, but also leads to the increase in elderly who need special care.., Causes of diseases are complex, but are mainly divided into hereditary and environmental factors. However, it is said that the rapid change was brought to us by the change of social environment, westernized life style, and rapidly aging population.

As you all know, lifestyle-related disease is related to obesity. It is speculated that insulin resistance, which is caused by obesity, promotes the lifestyle-related diseases. Adipose cells produce and secrete many substances (adipocytokines), which causes insulin resistance and/or promotes impaired glucose tolerance, high blood pressure, lipid metabolism disorder, and arteriosclerosis. Also at a molecular level, the function of enzymes such as PPARγ, PGC-1, SREBP-1c, as well as UCPs which reduces the lipid storage in tissues, GLUT4, and AMP kinase all gradually has become clear. National Institute of Health and Nutrition publishes many interesting findings which relates to these nutritional substances.

Diet and exercise are the fundamental treatments for lifestyle-related diseases. We need to give our patients a clear explanation about the merit of the diet and exercise and encourage them to change their life style. I think it is important to find out how and what kind of life style factors are related to cause which disease, at molecular, at cellular, at organ, and at individual levels.

Internationally, WHO points out that diabetic population will increase 1.9 times within 22 yeas in developing countries in Asia. Yet these countries have not fully developed a dietitian system and sometimes nutritional and dietetic policies are inadequate. I expect National Institute of Health and Nutrition to collaborate with these countries in develop their health promotion measures. I believe that this is what National Institute of Health and Nutrition is expected nationally, as well as from a global level, in addition to health promotion, prevention and medical solution of diseases.

Current Research Projects

Checking the data for the National Health and Nutrition Survey in Japan

Dr. Katsushi Yoshita (Head of Data Management for National Health and Nutrition Survey)

What do you imagine when you hear “checking the data”? Many of you would think of something like counting the check marks or numbers of multiple choices from the question sheets. However, “checking the data” for the National Health and Nutrition Survey in Japan is not that simple. The survey, which is based on the Health Promotion Law, is quite unique in comparison to other administrative surveys. We request over 5,000 households, to record the kind of food and their quantity the individual family members eat, and with the details such as how much soy sauce is used by a person, and so on. In addition, we hold the medical checkup site near the selected areas to get the survey subjects’ data on blood tests, blood pressure, and about drug use, etc… This complicated survey is stated as the mission of our institute in the law. We are required to “check” the complex and vast data of the survey.

Since the survey is annually conducted in November, at the Christmas season we receive the data sheets sent from health care centers of 300 areas all over Japan. Then a new year comes, we start the checking. First we check bunches of the papers if all are set in order because there are several varieties of records and survey sheets for each survey subject, and even one sheet can not be missed. After this simple but essential process, we start working on the complicated records of diet, and there we find simple mistakes, such as ages and sexes. When we go through more than 10,000 survey subjects’ data, we correct uncountable minor mistakes.

After these manual checking, we put these data into a computer. Step by step, the survey data are cleaned by a computer program and by registered dietitians, then finally, we can start the calculations. At last, about 12 months later the survey is done, the ministry of Health, Labor and Welfare announces “the summary of the National Health and Nutrition Survey in Japan” as you would read and hear on the news.

Because we handle huge records, the related process for checking, inputting, and tallying up is also enormous. To reduce the labor and increase the accuracy, we have developed the computer system which connects health care centers and NIHN. Thanks to this system, we now reduce much time comparing to several years ago. Our team of dietitians keep working hard to step up the system. I would be glad if you remember our staff’s such hard work when you have a chance to see the result of the National Health and Nutrition Survey in Japan.

Thoughts on Health and Nutrition Research

A Thought for Taking Diet

Dr. Kazuhiko Yamada (Director of Division of Applied Food Research)

It is wonderful if you can move your muscles without pain, have fulfilled feelings, being secured socially, and enjoy life with flexibility without being affected by inconvenient changes in environment. World Health Organization defines health as “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” in the preamble of its charter. We, as Japanese, can take phrase for granted, but not in many countries and areas in the world.

I received an e-mail from a friend who is working in Afghanistan as a JICA (Japan International Cooperation Agency) officer. In the letter he wrote; “ I wish you a happy new year! And no war on the Earth! Here we have an omen of reconstruction from the annihilation brought by the 20 years of war and 4 years of drought. I will keep working to help the recovery of Afghani farm villages this year as well. Every morning I have nan bread, eggs (boiled or omelet), cheese, and a cup of coffee or tea at the hotel. Tea in Afghanistan is usually green tea but it is a little different from a Japanese one. Lunch is served at the office and I have it with my colleagues. Menu is boiled vegetables on steamed rice and nan bread. Yesterday I had potatoes, cauliflower, beans, and carrot and green peas for today. When I told this to a person at JICA office he said ‘That’s all carbohydrate!’, but I do not care. Occasionally I am invited at the restaurant dinner with specialists. In Afghanistan, there are Afghan, Chinese, Italian, Western, and Indian cuisines. There is jiao-zi so called ‘mantou’ which is eaten with yoghurt in Afghanistan. That reminds me of ‘momo’, the Nepalese jiao-zi. Jiao-zi must come down along the silk road from China.” I felt the history and culture of food from his mail.

I participate in some committees of Codex Alimentarius as a part of my job. As this is an international meeting for food standardization, here we discuss on such issues, for instance, “Emphasis of nutritional functions of food” or “International unification of energy conversion on food labels”. Dietary fiber, for an example, is a hot topic because its definition and analysis methods are not universal. Some countries insist dietary fiber should be of plant-origin, on the other hand, some claim to add the fibers which is clear to have biological function by scientific evidence. Japan takes dietary fiber as a sum of food ingredient involving animal derived which is undigested by human digestive enzymes, and we undertake the analysis according to this definition. This kind of discussion influences standards of food intake, nutritional ingredients labelling, Standard Tables of Food Composition, and National Health and Nutrition Survey. Now I think we need to understand the international points of view.

In my graduate student days, I saw a picture at the front page of a text book of nutrition in the library. In the picture there were 26 smiling children from 26 different countries in their own traditional costumes. With the caption which reads “These children have different breakfasts in different cultures, but they are all healthy and growing well. The essence of nutrition is to find out what is in common.” When I attended the Asian Congress of Nutrition, in a workshop on diet in different countries at this conference, one speaker responded to a question asking back, “Do you mean change our diet?” Then the person who asked said, “No, no I mean modify the diet.” followed by a kind of softened atmosphere. I can imagine there are varieties of ways to promote health through healthy eating, under different cultural conditions.

Research Findings

Negative Balance of Calcium and Magnesium under Relatively Low Sodium Intake in Humans

Dr. Mamoru Nishimuta (Chief of Laboratory of Trace Element Metabolism, Division of Human Nutrition)

The sweat Na was relatively lower, but the sweat Ca and Mg were obviously higher during the previous experiment while taking a relatively low mineral diet with dietary Na of 100 mmol/d (or sodium chloride 6 g/d).

To explain these results, one assumption has been proposed. When Na reaches an insufficient level in the body, it is eluted from the bone where it is stored to compensate for any shortage. Then excess Ca and Mg may also be eluted along with the Na, and thus flow into the blood stream, and thereby inevitably cause a reduction of intestinal absorption as well as an increase in the urine excretion of these minerals. The aim of this study was to measure the balance of minerals (Na, K, Ca, and Mg) as well as to evaluate the hormones affecting the Na metabolism in humans under a low Na intake.

A 17-d metabolic study, including two successive balance sessions of 5 d, was designed. Six female students took part in this study after giving their written informed consent and also receiving a full explanation of the purpose and methods of this experiment.

During the period, starting from 6:00 a.m. on day 2 and ending at 8:30 a.m. on day 17, urine specimens were collected, and the 24-h urine excretion of minerals (Na, K, Ca, and Mg) was measured. On the morning of days 4, 9, and 14, the fasting morning blood was sampled, and the subjects also orally took a coloring marker for their feces (Carmine 0.5g) just before breakfast.

Three subjects pedaled a bicycle ergometer for 60 min once a day at the subject's selected intensity (1.25-1.5 kp, 50-60 rpm) during the first balance session. The other three subjects did the same during the second balance session. Arm sweat during exercise was collected after cleaning the skin surface.

The diets supplied during the experiment consisted of a five-day rotating menu and met all normal dietary allowances in Japan as calculated by the food tables. Fecal specimens were collected throughout the experiment and were separated into those originating in the diet during the first and second balance periods according to the ingested coloring marker appearing in the feces.

Samples were wet- ashed by hot plates using nitric acid and hydrogen peroxide, if necessary, and the minerals (Na, K, Ca, and Mg) were analyzed by an atomic absorption spectrophotometer.

Diet contained a relatively low Na (100 mmol/d or 2.2g/d) with adequate Ca (20 mmol/d or 800 mg/d) and Mg (12 mmol/d or 280 mg/d). Both the plasma renin activity (PRA) and aldosterone level were above the reference ranges throughout the experiment, which implied that the subjects were Na deficient. However, the urine Na excretion was about the same as that ingested, while there was no substantial reduction of sweat Na concentration observed during moderate physical exercise (13.2 ± 2.6 mmol/L) (mean ± SD). On the other hand, the urine Ca and Mg levels were high, but the apparent absorption of Ca and Mg was moderate (21 ± 5%, 34 ± 4%, respectively), which resulted in a negative balance of these two elements. It seems that the stored Na in the bone is eluted so as to compensate for the low dietary Na intake, while any excess Ca and Mg also inevitably flows into the blood stream with Na, which inhibited the intestinal absorption of both Ca and Mg and accelerates their excretion in urine.

Reference: Kodama N, Nishimuta M, Suzuki K. Negative balance of calcium and magnesium under relatively low sodium intake in humans. J Nutr Sci Vitaminol. 2003;49(3):201-9.

Research Findings

Regulatory sequence elements of GLUT4 gene expression in adipose tissues

Dr. Shinji Miura (Senior Researcher, Division of Clinical Nutrition)

Glucose transporter GLUT4 is mainly expressed in the muscles and adipose tissues, and takes an important role to maintain blood glucose level. Carbohydrates from food are decomposed into glucose and carried to blood. When blood sugar(=glucose) level gets higher, the pancreas secrete insulin which works on muscles and fat to activate GLUT4 to enhance glucose uptake in those tissues, so that the glucose level lowers. Under insulin resistant conditions, the effect of insulin in muscles is limited. Therefore, blood glucose level would not easily come down.

It is known that amount of GLUT4 in adipose tissue is reduced, when fatty meals (Westernized diet) is taken for a long period. Since the uptake of glucose mainly occurs in muscles, the insulin resistance in muscles has been the center of interest. However, as mice designed without GLUT4 in their adipose also showed the insulin resistance, it is now speculated that the reduction in the development of GLUT4 in adipose tissue, also relates significantly to the onset of diabetes.

In our laboratory, we have studied genes which control the amount of GLUT4 expression. We have developed transgenic GLUT4 genes containing GLUT4 coded genes and different lengths of promoter sequences. Then we put the transgenic GLUT4 gene into fertilized mice eggs, so that in some cases mice with transgenic genes were born. By examining the expression of transgenic GLUT4 in adipose tissue in these mice, we have found out what length of the region in the gene is needed for GLUT4 expression in adipose tissue.

Consequently, now we have succeeded to narrow the gene areas between adipose tissue specific elements (ASE) and high-fat responsive elements (HFRE). We have found the nucleoprotein X which bind to ASE and its DNA sequences as well.

We are planning to ascertain DNA sequences of ASE and HFRE, then identify the transcription factors for controlling the development of nucleoprotein. If it comes clear that these transcription factors controls the development of GLUT4 in adipose, it may help to create new treatments for diabetes.

Reference: Miura S, Tsunoda N, Ikeda S, Kai Y, Ono M, Maruyama K, Takahashi M, Mochida K, Matsuda J, Lane MD, Ezaki O. Regulatory sequence elements of mouse GLUT4 gene expression in adipose tissues. Biochem. Biophys. Res. Commun. 2003; 312:277-284.

Research Findings

How much exercise is required to reduce blood pressure in essential hypertension?

Dr. Kazuko Takata (Senior Researcher, Division of Health Promotion and Exercise)

It is well known that exercises helps to improve mild high blood pressure. Then, how much exercise reduces how much blood pressure? This survey was undertaken in order to discuss and figure out the appropriate momentum and frequency of exercise.

This study was done to examine the efficiency of exercise against mild chronic diseases, in which 1,425 subjects worked out for 8 weeks under the supervision of experts to observe the change of the disease condition. There were 450 subjects with high blood pressure (categorized in Stage1 and 2). We analyzed 207 subjects' data with the exception of those who were under medical treatment of high blood pressure and/or coronary artery diseases, or had exercise habits. Before and after the 8-week training period, height, weight, blood pressure, blood tests and dietary intakes and physical fitness survey were taken. Those who were in the exercise group had worked out under expert guidance at a cooperated sports gym. The exercise was the combination of warm-up, stretching, aerobic and muscular exercise. The intensity of aerobic exercise was set to the 50% of maximal oxygen uptake. On the other hand, the control group kept the daily physical activity without any special work outs.

Then the exercise group was divided into four groups according to their amount of work out time (30~60mins, 61~90mins, 91~120mins, over 120mins) in a week. The average systolic blood pressure was the same in each group before the training period. After 8 weeks, systolic and diastolic pressure of the control group did not change. However, all four exercise groups reduced their blood pressure. Compared to the 30~60mins group, systolic blood pressure was improved quite much in 61~90mins group, but we did not find outstanding difference between 61~90, 91~120, and over 120 groups.

Also we compared the frequency of the work out as 1~2times, 3~4times, over 5times per week, and checked the change in blood pressure. As a result, those who worked out over 61mins in total in a week, reduced his/her blood pressure despite the frequency.

Now it is clear that;

1) If a mild high blood pressure person works out over 61mins per a week, he/she will reduce his/her pressure more than 10mmHg in 8 weeks.

2) The efficiency of the exercise does not differ according to the frequency if one keeps over 61mins exercise in total in a week.

Reference: Ishikawa-Takata K, Ohta T, Tanaka H. How much exercise is required to reduce blood pressure in essential hypertensives: a dose-response study. Am J Hypertens. 2003 ;16(8):629-33.

Developing a functional structured lipid efficient for the prevention of life-style related disease

Dr. Junichi Nagata (Chief of Laboratory of Nutritional Assessment of Food Components, Division of Food Science)

Although you have not heard a term “Structured Lipid”, it becomes more and more familiar to our daily diet. In general, lipids are structured by 3 fatty acids attaching to a glycerol. The fatty acids attached to the sn-1, 3 positions of the glycerol are hydrolyzed by digestive enzymes, and a mono-glycerol and two fatty acids are formed. “Structured Lipid” is the physiologically advantaged lipid using the biological feature of lipids, to take in this multi-functioning acid effectively into the body.

At the present time, there are mainly two types of structured lipids in Japanese market. One is made to combine a random fatty acid at a random position of glycerol to bring out the functions of the fatty acid most effectively. The other is processed in a unique form for absorption by contriving numbers or combining positions of fatty acids. In the market, you can find di-acylglycerol as edible lipids or synthesized oil from medium chain fatty acid and edible lipids, as examples of structured lipids.

In the present study, we have synthesized four new structured lipids by using the sn-1, 3 specific lipase. Each lipid includes medium chain fat acid C8:0 or C10:0 and functionally unique with combination of linoleic acid. Then we started the study in the purpose of examining the effects of highly purified structured lipids on serum and liver lipid profiles in rats. We also investigated in vitro hydrolysis of lipid emulsions by porcine pancreas.

M-L-M types of structured lipid (medium chain fat acid at sn-1, 3 positions and linoleic at sn-2 position of glycerol) were 2 to 3 times higher than those of L-M-L types (linoleic at sn-1, 3 positions and medium chain at sn-2 position). The diet containing structured lipids or corn oil was administrated to rats for 4 weeks. There were no significant differences in growth and food efficiency. Serum cholesterol levels were significantly lower in L-8-L, 10-L-10 and L-10-L groups than in the corn oil groups. Serum triglyceride levels were significantly lower in rats fed L-M-L types than those in other groups. Serum non-esterified fatty acid (NEFA) and beta-hydroxybutylate levels were significantly higher in rats fed M-L-M types than those of the other groups. These results show that the feeding of highly purified L-M-L types could effectively improve serum and liver lipid profiles and that M-L-M types may be a preferable substrate for the pancreas and contribute energy supply in rats. Also it shows that M-L-M type structured lipids show high affinity for digestive enzymes, and have remarkable function on energy substrate and supply of essential fatty acid.

The biological efficiency of lipids is thought to be indicated that there are some possibilities to be affected by its basic structure of triglyceride, not only by the efficiency brought by fatty acids. Thus, we expect to develop various combinations of functional fatty acids for the purpose of prevention and improvement of life-style related disease.

Reference: Nagata J, Kasai M, Watanabe S, Ikeda I, Saito M. Effects of highly purified structured lipids containing medium-chain fatty acids and linoleic acid on lipid profiles in rats. Biosci Biotechnol Biochem. 2003 ;67(9):1937-43.