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ABSTRACT

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Current Status of Cadmium Exposure among Japanese, Especially Regarding the Safety Standard for Cadmium Concentration in Rice and Adverse Effects on Proximal Renal Tubular Function Observed in Farmers Exposed to Cadmium through Consumption of Self-Grown Rice

Nippon Eiseigaku Zasshi, 67, 447–454 (2012)
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Because the staple food in Japan is rice, which absorbs cadmium (Cd) from the soil efficiently, rice is the main source of exposure to Cd in the Japanese population. In addition, there have been many Cd-contaminated farming areas in Japan. Therefore, a safety standard for the Cd concentration in rice was set as 0.4 ppm by the Japanese government. This safety standard has been followed for decades without any appropriate scientific or legal basis. However, recent epidemiological studies of female Japanese farmers exposed to Cd through self-grown rice, that is, a series of Japanese Multi-centered Environmental Toxicant Study (JMETS), showed evidence that the safety standard is appropriate. Therefore, general Japanese consumers are unlikely exposed to Cd excessively with the application of this safety standard, considering the trend of decreasing amount of rice consumed among the Japanese population. On the other hand, Japanese farmers were found to be at risk of Cd exposure through the consumption of self-grown rice with a high Cd concentration. Actually, the JMETS showed that female farmers at 70 years of age or older had a decreased proximal renal tubular function due to the high renal accumulation of Cd. On the basis of these findings, "medical examinations for Cd exposure" have recently been implemented for farmers residing in Cd-polluted areas in northern Japan. Because it has been estimated that such Cd-polluted areas are actually larger, it is necessary to implement medical examinations of more farmers there, particularly the elderly.

Itai-Itai Disease: Cadmium-Induced Renal Tubular Osteomalacia —Current Situations and Future Perspectives

Nippon Eiseigaku Zasshi, 67, 455–463 (2012)
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Cadmium (Cd) is one of the most toxic elements to which humans could be exposed at work or in the environment. The outbreak of *itai-itai* disease, which is the most severe stage of chronic Cd poisoning, occurred in the Cd-polluted Jinzu River basin in Toyama. In this area, the river was contaminated by slag from a mine upstream; as a consequence, the soil in rice paddies was polluted with heavy metals including Cd through irrigation water from around 1910 to the 1960s. The government of Toyama prefecture carried out an extensive survey on Cd concentration in rice and soil of the paddy fields and declared that the upper layer of a total of 1500 ha of paddy fields should be replaced by nonpolluted soil. Then, an intervention program of soil replacement in the polluted paddy fields was continually carried out from 1980 to 2011. As a result, Cd concentration in rice markedly decreased. The kidney is the organ critically affected after long-term exposure to Cd. Proximal tubular dysfunction (RTD) has been found among the inhabitants of the Jinzu River basin. The very recent report by the Environmental Agency in Japan in 2009 has disclosed that β2-microglobulinuria with RTD is still found at a high prevalence among the inhabitants of the Jinzu River basin of both sexes. Twenty patients with *itai-itai* disease (1 male and 19 females), who attended our hospital and received medical examination during 2000–2008, had applied for recognition as *itai-itai* disease patients to the government of Toyama prefecture. In this paper, the recent epidemiological and clinical features of *itai-itai* disease are discussed on the basis of a review of the cases of these 19 female patients.

Fibroblast Growth Factor 23 Mediates the Phosphaturic Actions of Cadmium

Nippon Eiseigaku Zasshi, 67, 464–471 (2012)
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Phosphaturia has been documented following cadmium (Cd) exposure in both humans and experimental animals. Fibroblast growth factor 23 (FGF23) serves as an essential phosphate homeostasis pathway in the bone-kidney axis. In the present study, we investigated the effects of Cd on phosphate (Pi) homeostasis in mice. Following Cd injection into C57BL/6J mice, plasma FGF23 concentration significantly increased. The urinary Pi excretion level was significantly higher in the Cd-injected C57BL/6J mice than in the control group. Plasma Pi concentration decreased only slightly in the Cd-injected mice compared with the control group. No changes were observed in the concentration of the plasma parathyroid hormone and 1,25-dihydroxy vitamin D_3 in both groups of mice. We observed a decrease in phosphate transport activity and also a decrease in the expression level of renal phosphate transporter Npt2c, but not that of Npt2a. Furthermore, we examined the effect of Cd on Npt2c in Npt2a-knockout (KO) mice, which expresses Npt2c as a major NaPi cotransporter. Injecting Cd to Npt2aKO mice induced a significant increase in plasma FGF23 concentration and urinary Pi excretion level. Furthermore, we observed decreases in phosphate transport activity and renal Npt2c expression level in the Cd-injected Npt2a KO mice. The present study suggests that hypophosphatemia induced by Cd may be closely associated with FGF23.

Cadmium Induces p53-Dependent Apoptosis Through the Inhibition of *Ube2d* Family Gene Expression

Nippon Eiseigaku Zasshi, 67, 472–477 (2012)
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Cadmium (Cd), a harmful metal, exerts severe toxic effects on various tissues such as those in the kidney, liver, lung, and bone. In particular, renal toxicity with damage to proximal tubule cells is caused by chronic exposure to Cd. However, the molecular mechanism underlying chronic Cd renal toxicity remains to be understood. In this review, we present our recent findings since we examined to search for the target molecules involved in the renal toxicity of Cd using toxicogenomics. In NRK-52E rat renal tubular epithelial cells, we found using DNA microarrays that Cd suppressed the expression of the gene encoding Ube2d4, a member of the Ube2d family. The Ube2d family consists of selective ubiquitin-conjugating enzymes associated with p53 degradation. Moreover, Cd suppressed the expressions of genes encoding all Ube2d family members (Ube2d1/2/3/4) prior to the appearance of cytotoxicity in NRK-52E cells. Cd markedly increased p53 protein level and induced p53 phosphorylation and apoptosis in the cells. In vivo studies showed that chronic Cd exposure also suppressed *Ube2d* family gene expression and induced p53 accumulation and apoptosis in the renal tubules of the mouse kidney. These findings suggest that Cd causes p53-dependent apoptosis due to the inhibition of p53 degradation through the down-regulation of *Ube2d* family genes in NRK-52E cells and mouse kidney. Thus, the *Ube2d* family genes may be one of the key targets of renal toxicity caused by Cd.

Reducing Cadmium Content of Rice Grains by Means of Flooding and a Few Problems

Nippon Eiseigaku Zasshi, 67, 478–483 (2012)
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The effects of water management in rice paddies on the levels of cadmium (Cd) and arsenic (As) in Japanese rice grains were tested. In order to reduce the Cd concentration in rice grains, flooding for 3 weeks before and after heading was most effective, but this treatment increased As concentration considerably. Aerobic treatment was effective in reducing As concentration in rice grains, but increased Cd concentration markedly. In the pot experiment, flooding treatment after heading was more effective than flooding treatment before heading in reducing both Cd and As concentrations in rice grains. The concentration of dimethylarsinic acid (DMA) in rice grains was very low under aerobic conditions, but increased in the continuous-flooding treatment. In the field experiment, the grain As concentration in the case of flooding for 3 weeks before and after heading was higher than that in the case of intermittent irrigation. The ratios of DMA to the total As concentration were 3–52 % in the pot experiment and 7–13 % in the field experiment.

Re-evaluation of the Fundamentals of Trace Elements

Nippon Eiseigaku Zasshi, 67, 484 (2012)
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The roles of trace elements have been extensively studied for decades. However, recent advances in both molecular and epidemiological studies on trace elements have provided new information and concepts on the actions of trace elements. Some of our fundamental knowledge on the roles of trace elements based on classical data should be replaced by new concept based on new findings. This series of "Re-evaluation of the Fundamentals of Trace Elements" aims to provide new fundamentals on trace elements by reviewing rapidly advancing knowledge in this study area. The first article is a critical review on the role of chromium in human nutrition.

Is Chromium an Essential Trace Element in Human Nutrition?

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It has been recognized that chromium is an essential trace element associated with carbohydrate metabolism, and chromium deficiency

causes an impaired glucose tolerance. Recently, however, Vincent et al. have reported that chromium is not an essential trace element. In the present report, the author evaluated the nutritional essentiality of chromium by reviewing several previous reports. In almost all previous reports, the chromium concentration in the animal feed used was higher than 0.1 μg/g, and it is difficult to consider that the experimental animals were in a low-chromium state. In addition, the amount of chromium administered to the animals for the improvement of glucose tolerance was at a pharmacological level, and corresponded to a level that far exceeded the human daily chromium intake (20–80 μg/day). On the other hand, recent research has clearly shown that feeding with a severely low-chromium diet (0.016 μg/g) does not impair glucose tolerance. The amount of chromium absorbed in humans estimated from chromium intake (20–80 μg/day), chromium absorption rate (1 %), and urinary chromium excretion (<1 μg/day) is less than 1 μg/day, which is much lower than those of other essential trace elements. In addition, because there is an inconsistency between the chromium concentration in food and chromium intake, chromium intake seems to be dependent on chromium contamination during food processing and cooking. It is concluded that there is a high possibility that chromium is not an essential trace element.

Association between Sleep Quality and Life Function among Elderly Community Residents

Nippon Eiseigaku Zasshi, 67, 492–500 (2012)
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Objective: To investigate the association between sleep quality and life function in an elderly Japanese population.
Methods: A total of 563 residents of a village in Kumamoto Prefecture aged ≥65 years were asked to fill out a self-administered questionnaire survey from June to July 2010. Sleep quality and life function were respectively evaluated using the Pittsburgh Sleep Quality Index (PSQI) and Basics Check List, which is used to screen elderly individuals at high risk of needing long-term care in the future. As adjustment factors, age, sex, economic situation, residency status, medical history, depression status, and cognitive function were assessed. We examined the relationship between sleep quality and life function using multiple logistic regression analysis, with life function as a dependent variable. Subjects already receiving care or with psychiatric disorders or severe cognitive disturbance were excluded from analysis.
Results: Among the subjects ($n = 395$), a significant relationship was found between poor sleep quality and impaired life function in all models. The odds ratio was 1.82 (95 % confidence interval 1.03–3.23) in the final model controlling for all adjustment factors.
Conclusions: Our findings here suggest a significant relationship between poor sleep quality and impaired life function among elderly community residents. Given these findings, intervention to improve sleep may help delay or prevent the need for long-term care among elderly individuals.

Effect of Large-Scale Repair Work on Indoor Formaldehyde Levels and Subjective Symptoms in Medical Students during Gross Anatomy Dissection Course

Nippon Eiseigaku Zasshi, 67, 501–507 (2012)
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Objectives: To examine the effect of large-scale repair work on indoor formaldehyde (FA) levels and subjective symptoms in medical students during a gross anatomy dissection course.
Methods: We measured the indoor FA levels, room air temperature, and room humidity during a gross anatomy dissection course. In addition, the prevalence of subjective symptoms, keeping allergy state, and wearing personal protective equipment were surveyed in two groups of students using a self-administered questionnaire.
Results: The mean indoor FA levels before and after repair work were 1.22 ppm and 0.14 ppm, respectively. The mean indoor FA level significantly decreased after repair work. The prevalences of most subjective symptoms before the anatomy practice were similar before and after the repair work. However, the prevalences of most subjective symptoms during the anatomy practice were lower after the repair work.
Conclusions: The mean indoor FA levels and prevalences of subjective symptoms decreased after the repair work. We have to continuously monitor indoor FA levels, carry out private countermeasures to minimize exposure to FA, and maintain equipment for ventilation to be able to conduct practice in a comfortable environment.

Acute Mild Hypoxia Impairs Dynamic Cerebral Autoregulation Assessed by Spectral Analysis and Thigh-Cuff Deflation

Nippon Eiseigaku Zasshi, 67, 508–513 (2012)
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Objectives: Acute hypoxia may impair dynamic cerebral autoregulation. However, previous studies have been controversial. The difference in methods of estimation of dynamic cerebral autoregulation is reported to be responsible for conflicting reports. We, therefore, conducted this study using two representative methods of estimation of dynamic cerebral autoregulation to test our hypothesis that dynamic cerebral autoregulation is impaired during acute exposure to mild hypoxia.
Methods: Eleven healthy men were exposed to 15 % oxygen concentration for 2 h. They were examined under normoxia (21 % O_2) and hypoxia (15 % O_2). The mean arterial pressure (MAP) in the radial artery was measured by tonometry, and cerebral blood flow velocity (CBFv) in the middle cerebral artery was measured by

transcranial Doppler ultrasonography. Dynamic cerebral autoregulation was assessed by spectral and transfer function analyses of beat-by-beat changes in MAP and CBFv. Moreover, the dynamic rate of regulation and percentage restoration of CBFv were estimated when a temporal decrease in arterial pressure was induced by thigh-cuff deflation.

Results: Arterial oxygen saturation decreased significantly during hypoxia (97 ± 0–88 ± 1 %), whereas respiratory rate was unchanged, as was steady-state CBFv. With 15 % O_2, the very-low-frequency power of CBFv variability increased significantly. Transfer function coherence (0.40 ± 0.02–0.53 ± 0.05) and gain (0.51 ± 0.07–0.79 ± 0.11 cm/s/mmHg) in the very-low-frequency range increased significantly. Moreover, the percentage restoration of CBF velocity determined by thigh-cuff deflation decreased significantly during hypoxia (125 ± 25–65 ± 8 %).

Conclusions: Taken together, these results obtained using two representative methods consistently indicate that mild hypoxia impairs dynamic cerebral autoregulation.

Perspective on the Nuclear Power Plant Accident Caused by the Great East Japan Earthquake and Tsunami: Health Impairment Risks due to Pollution by Radioactive Materials from the Damaged Plant as Recognized by Experts and by the General Population and Role of the Experts

Nippon Eiseigaku Zasshi, 67, 514–523 (2012)
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Introduction: Large amounts of radioactive materials were leaked into the environment from the Fukushima Daiichi Nuclear Power Plant (FDNPP) of the Tokyo Electric Power Company damaged by the 2011 Great East Japan Earthquake and accompanying tsunami. Increased health impairment risks due to the leaked radioactive materials are of concern over a long period of time and over a wide geographical area. From the results of epidemiologic studies conducted after the Chernobyl accident, the health risks are not anticipated to be very marked. The purpose of the present study is to examine (1) the elevated health risks as viewed by the general population, (2) tolerance to the risks that the general population suffer from their viewpoint, and (3) the overall picture as seen by researchers and experts in specialized areas of study after the accident.

Method: Information was obtained from articles in print and on the Internet and by interviewing a psychologist and tens of employees of several corporations.

Results and discussion: Epidemiologic studies conducted after the severe accident of the nuclear power plant in Chernobyl revealed an elevated risk of thyroid cancer in children due to ^{131}I while elevated risks due to radioactive materials other than ^{131}I were not detected. The amount of radioactive materials leaked into the environment from the FDNPP was less than that in Chernobyl. Therefore, it is possible to estimate that health impairment risks due to the leaked radioactive materials from the FDNPP are low. However, it is impossible to conclude a zero risk. It is likely that the general population does not fully understand the health impairment risks due to the leaked radioactive materials from the FDNPP. Although no increased incidences of diseases other than thyroid cancer of children were scientifically shown en masse from studies in Chernobyl, individual risks and results in the future caused by the severe accident of FDNPP cannot be denied.

Much of the general population is apt to demand the security of a zero risk from human-generated disasters such as the severe accident of FDNPP. Many are very intolerant of the health impairment risks factors and wish to avoid any risk altogether. The viewpoint of the general population differs considerably from that of epidemiologists and other research experts.

Researchers and experts are often well versed in their own specialized areas but ignorant of other areas. Thus, it is difficult to grasp the complete view of an event under consideration. This so-called '*takotsubo*' situation is dangerous in human society. Researchers and experts must make effort to understand areas other than their own specialized areas. Scientific researchers usually possess a great deal of conviction from the results of their own studies. They are apt to ignore criticism of their study results from individuals working in other research areas even when the results of their studies are inadequate. When the conditions of their studies are changed somewhat and insufficient information is obtained, the results may not be accurate. Researchers and experts should take full cognizance of this possibility, view with strong skepticism about the results of studies even in their own areas, and listen with humility to criticisms from those working in fields of discipline other than their own.

Conclusions: It should be fully recognized that the viewpoint of the general population is considerably different from that of researchers and experts regarding health risks due to the severe accident of FDNPP. Researchers and experts must make effort to understand the opinions of those working in areas other than their own in order to grasp a true and complete view of an event under consideration.