

Epidemiological Follow-up Study On Tubular Proteinuria Among People Living In Cadmium Polluted Area In Toyama, Japan.

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ABSTRACT

Epidemiological follow-up studies were carried out to clarify the process and prognosis of renal tubular dysfunction induced by cadmium(Cd) among the people living in Cd-polluted area in Toyama Prefecture, Japan.

The concentrations of β_2 -microglobulin (B-m) were measured among family members of Itai-itai disease patients in 1975 and 1985. The data of 93 persons (43 men, 50 women) were compared in 1985 with those of 1975. Some of them were again compared in further studies up to 1990.

β_2 -microglobulinuria (B-microglobulinuria) were observed more frequently in those persons over 40 years of age than in those who are younger. The concentrations of urinary B-m show similar values in 1975, 1985 and 1990. Itai-itai disease (osteomalacia) had developed in a woman who exhibited severe B-microglobulinuria during this 15 year period. There were some cases, however, which showed a decrease of urinary B-m concentrations in young people who had not been exposed to heavy dosages of Cd.

These results indicate that the renal tubular damage by Cd increases or persists over a long period of time and a long follow-up study is necessary to prevent osteomalacia and its severe health effects.

INTRODUCTION

In the industrialization of modern society, many environmental problems have resulted, which affects not only urban populations but rural communities as well. Japan is no exception. One of the most important environmental problems and the subject in this paper is cadmium (Cd) contamination in a rural agriculture area.

There are various locations heavily contaminated with Cd throughout Japan. One of the most contaminated areas is located along the Jinzu River in Fuchu Machi of Toyama Prefecture. It is located on the west coast-side of Honshu Island. There is a large mine which produces lead, Zinc and Cd, located on the upper reaches of the Jinzu River. Before and during

World War II, rapid increases in the production of these metals led to the faulty treatment of waste water and discharging its waste into the upperstream of the Jinzu River. The river became markedly polluted with poisonous waste metals such as Cd and zinc. The waste Cd increased again during Japan high economic growth period between 1950 and 1970 (Kurachi,1980). The Cd contamination is thought to be major causative agent of the endemic disease which is called Itai-itai.

Fig. 1 shows the location of the endemic area of the Itai-itai disease and the concentrations of the rice field soil samples measured between 1984 and 1985. The Cd concentrations of the soil samples in the endemic area showed higher levels than those soil samples in the surrounding area though a small number of the samples collected around the river mouth, show high levels. Fig.2 shows the long term fluctuations of the Cd concentration discharged in the Jinzu River measured by the monitoring system supported by the

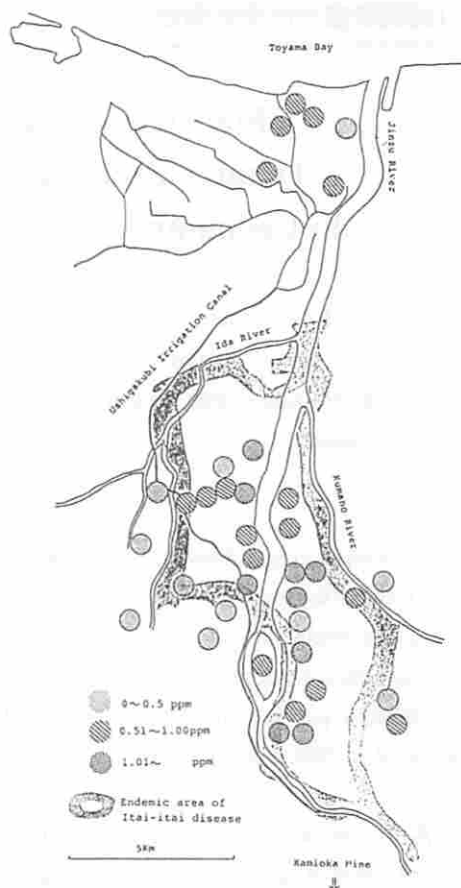


Fig. 1 Location of the endemic area of Itai-itai disease and concentrations of cadmium in rice field soil.

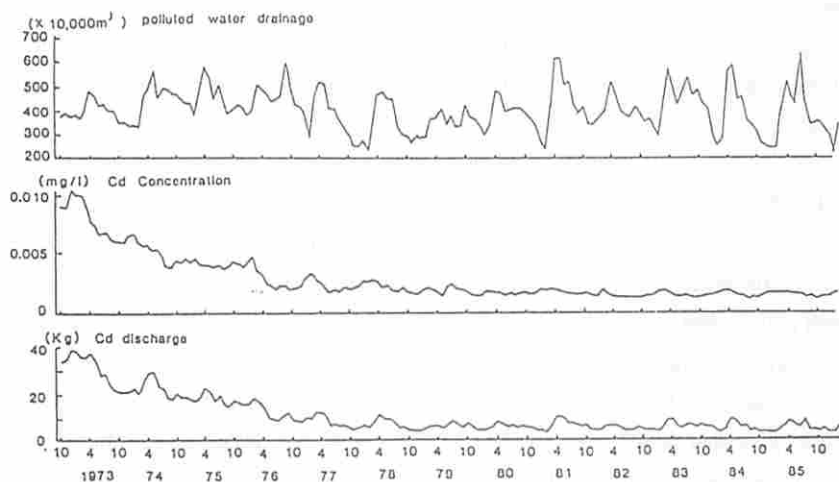


Fig. 2 Changes of Cd polluted water drainage, Cd Concentration and Cd discharge.

Kamioka Mine. The Cd discharge from mine decreases significantly from 1973 through 1985 though the Cd discharge increases in small amounts during the rainy season.

MATERIALS AND METHODS

We performed an epidemiological survey on the family members of the Itai-itai disease patients in 1975 and 1985. The number of participants examined in both examinations was 93 (43 men and 50 women). In both examinations, morning urine specimens were obtained from each participant. Urine samples for the measurement of β_2 -microglobulin (B-m) were kept at about pH 7.0 by adding phosphate buffer solution and kept frozen at -20°C . B-m was measured by radioimmunoassay in 1975 (Kanai et al., 1976) and by latex immunoassay in 1985 (Kasuya et al., 1986).

24 persons ranging in age from 20 to 69 years were studied in 1975, with follow-up studies in 1983, 1985 and 1990. B-m was measured by radioimmunoassay in 1975,

by latex immunoassay in 1985 and by enzyme immunoassay in 1983 and 1990. Cadmium in urine samples was measured by flameless atomic absorption spectrophotometry in 1983. Albumin was measured by single radial immunodiffusion method in 1975, 1983 and 1985. During the follow-up study, a female patient developed osteomalacia (Itai-itai disease). We observed clinical and laboratory findings in this patient such as serum calcium and phosphorus levels.

RESULTS

Fig. 3 shows the relationship of the concentrations of urinary B-m and age in 1975. Persons who showed high levels of urinary B-m (>1 mg/g.cr) increase rapidly after 40 years of age. Persons who showed the highest levels of urinary B-m (>10 mg/g.cr) were 60 years of age or older. In a 1985 survey, persons who showed high levels of B-m exhibited similar high levels of B-m in urine samples. For that reason, the similar relationships were observed

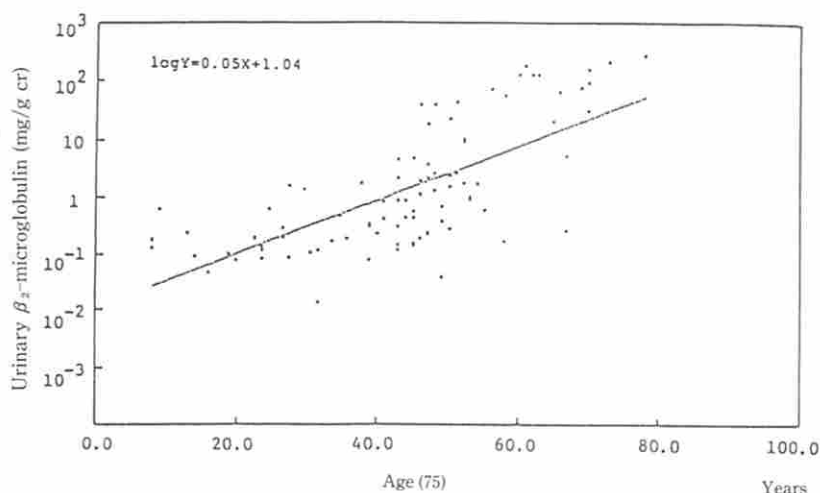


Fig. 3 Urinary β_2 -microglobulin levels according to age (1975).

between the concentrations of B-m and the age except in the age shift of 10 years.

To clarify the long term fluctuation of B-m, 24 persons of ages 20 to 69 were followed up. Fig. 4 shows overall fluctuation of urinary B-m between 1975 and 1990. 13 persons participated in each survey but unfortunately the other persons were absent from one or two surveys. However it is obvious that overall fluctuations of urinary B-m are small. An increasing tendency, however, was observed among a group of persons who showed the urinary B-m levels above 1 mg/g.cr in 1975. This suggests that the tubular

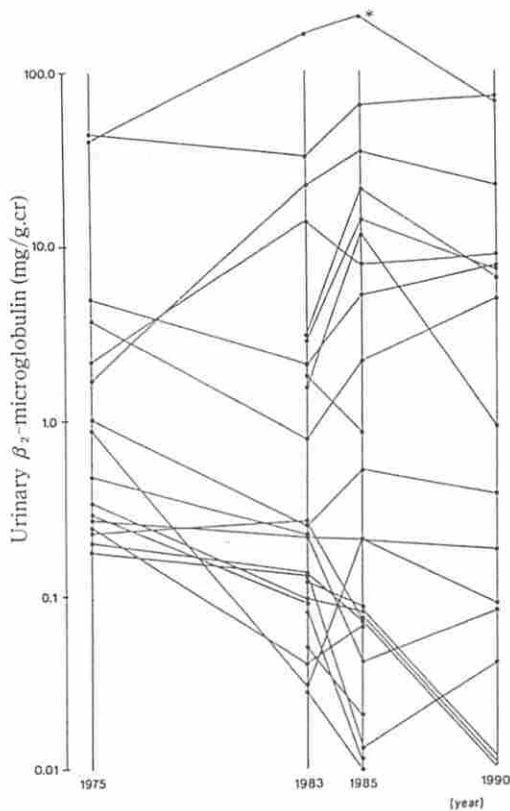


Fig. 4 Fluctuations of urinary β_2 -microglobulin from 1975 through 1990.

* New occurrence of Itai-itai disease

dysfunction persists and becomes worse over a long period of time. On the other hand, a decreasing tendency was observed among persons whose urinary B-m was lower or about 1 mg/g.cr in 1975 although the changes of urinary B-m were not as great. Significant difference was observed between the Cd levels of these two groups. The mean concentrations of the Cd in the urine samples in the former and the latter were 20.5 ug/g.cr and 7.4ug/g.cr respectively.

Fig. 5 shows the characteristics of the electrophoretic pattern of the urine proteins of Itai-itai disease using agarose gel methods. In the urine of the Itai-itai disease, not only B-m but also albumin and other proteins obviously exist in higher levels than normal. This suggests that relatively high molecular weight protein like albumin excrete in the urine of Itai-itai patients by tubular dysfunction.

Fig. 6 shows the relationships between the changes of B-m and albumin in urine samples from 1975 through 1985. The number of subjects examined was 19, including 3 Itai-itai patients and one new occurrence case of the disease. As an overall tendency, the concentrations of albumin increased according to the concentrations of B-m. Three Itai-itai disease patients show consistently the highest level in both B-m and albumin. Increasing tendencies and large fluctuations of albumin were observed among some persons whose B-m levels were above 1 mg/g.cr especially in the new occurrence case. On the other hand, those who showed lower concentrations of B-m than 1 mg/g.cr exhibit a decreasing tendency in both B-m and albumin. Fluctua-

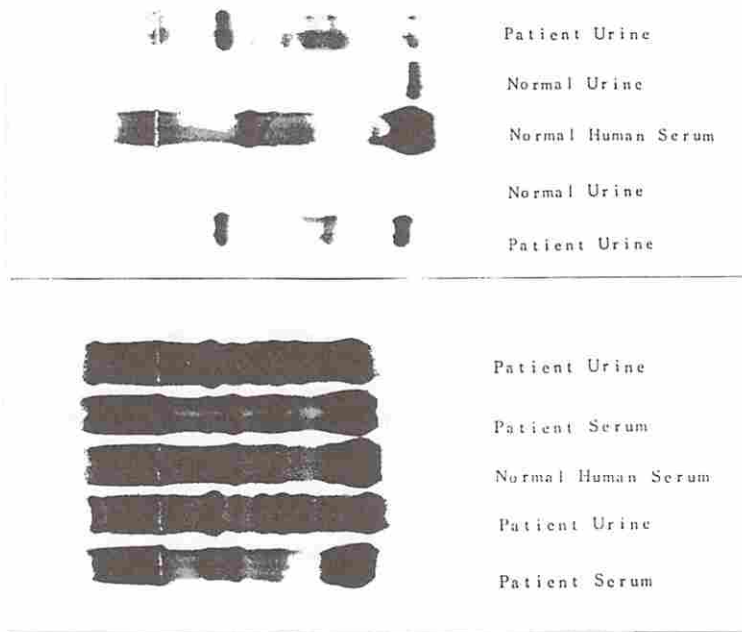
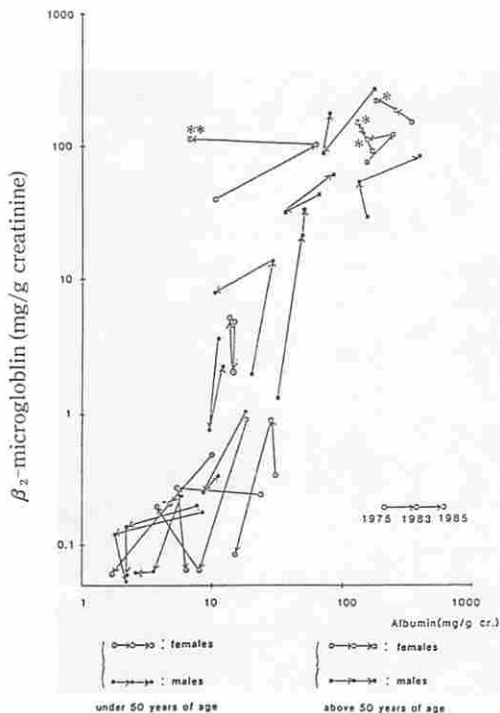


Fig. 5 Electrophoretic pattern of the urine protein of Itai-itai disease.



* Itai-itai disease ** New occurrence of Itai-itai disease

Fig. 6 Relationships between the changes of β_2 -microglobulin and albumin.

tions of the albumin concentrations seems to be a sign of the progress of renal deterioration.

Fig. 7 shows the changes of laboratory findings such as serum levels of calcium, phosphorus and creatinine in the new occurrence case of the Itai-itai disease. She is a woman, who in 1975' 46 years of age and who had lived in Fuchu Machi from birth. As she lived and farmed this area, she was exposed high levels of Cd intake for a long period of time. She began to suffer from lumbago and lower extremity pain in 1979. She consulted a doctor and received some analgesic medication. However, symptoms such as lumbago and severe extremity pain persisted. Her urinary concentration of B-m increased from 1975 through 1985 and showed its highest peak in 1985 (110.9 mg/g.cr).

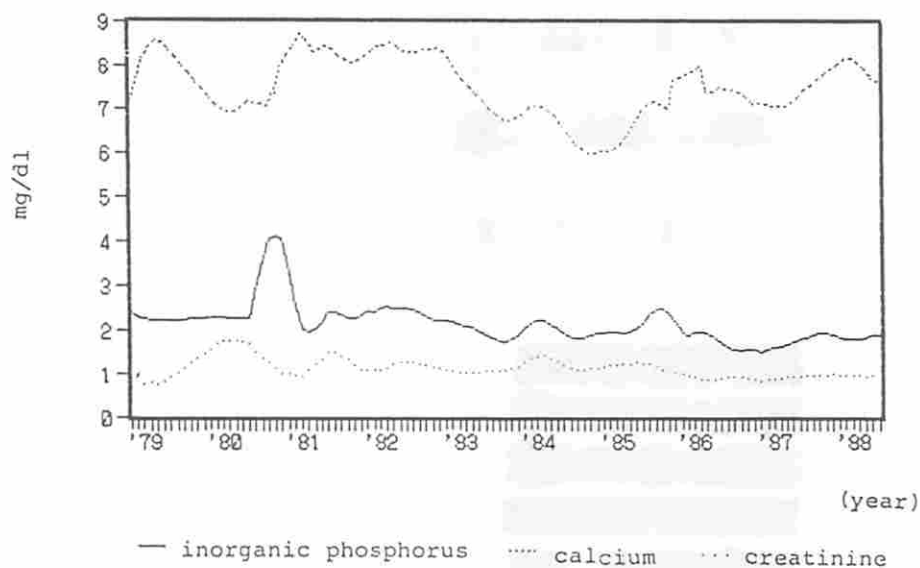


Fig. 7 Changes of serum calcium, phosphorus and creatinine.

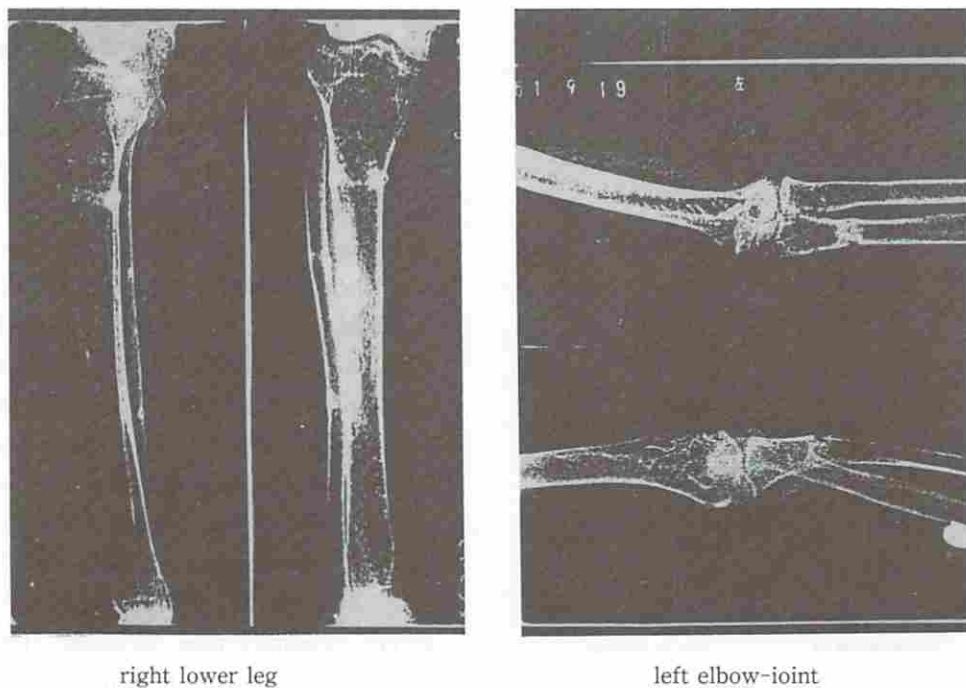


Fig. 8 Roentgenological findings of the bone change.

Serum calcium shows lower levels than normal in 1979 and continued to show rapid decreasing tendencies through 1988. Serum phosphorus showed also a lower level than normal in 1979 and showed decreasing tendencies there after. Serum alkaline phosphatase showed continuously a higher level than normal although serum creatinine is within a normal range. Pathological fractures, shown in Fig. 8, developed in the upper and lower extremities of the patient and she was officially recognized as a new occurrence case of Itai-itai disease in 1986 by the Toyama Prefectural Medical Committee for Diagnosis.

DISCUSSION

Itai-itai disease was discovered in 1946 among the people living along Jinzu River basin. The clinical signs and symptoms may be characterized as renal tubular dysfunction and osteomalacia, which bring severe pain and pathological fractures to various parts of the body. Before Cd was found as a causative agent of the Itai-itai disease, some nutritional deficiencies or traditional life styles of the farmers were suspected to be causal factors of the disease (Kobayashi, 1970).

After the Research Committees supported by the Japanese Government began investigations on the Itai-itai disease in 1963, some important characteristics of the disease were clarified including the regional restriction of the distribution of the Itai-itai patients. High prevalence was found in the area of highest Cd contamination along the Jinzu River basin (Kato et al., 1968). Consequently in 1968, the Ministry of Health and Welfare made an official

announcement concerning the causal relationship between Cd and the Itai-itai disease on the basis of these epidemiological studies. There are, however, some questions and controversies about the Itai-itai disease and Cd as valuable data are lacking on the long term health effects of environmental exposure to Cd.

We performed investigations to clarify long term effects of Cd, especially process and prognosis of the renal tubular dysfunction known as a preclinical change induced by Cd intake. We compared the urinary B-m concentrations between surveys in 1975 and 1985. We found that the fluctuations of urinary B-m was relatively small over the ten year-period and persons who showed high levels of urinary B-m in 1975 still show high level of B-m in 1985. In these persons, renal tubular dysfunction persisted and became more aggravated over a long period of time. This finding corresponds with the findings reported by Roels et al. (1982). Elinder et al. (1985) and Kido et al. (1988). To clarify in more detail, 24 persons ranging from 20 to 69 years of age were studied in 1975, with follow-up studies in 1983, 1985 and again 1990. These persons lived in the central region of the polluted area and were much exposed to Cd. In our study, unfortunately, we were not able to conduct uniform methods in measuring urinary B-m in every follow-up survey because of the changing technical renovation of new measuring equipment and the danger to technicians using isotopes. However, we found very close correlations between radioimmunoassay and enzymeimmunoassay (correlation coefficient : $r=0.99$, $p<0.001$) or latex immunoas-

say ($r=0.99$, $p<0.001$).

We found that persons who showed high levels of urinary B-m in 1975 showed continuously high levels and increasing tendencies of urinary B-m through 1990. As these persons showed higher levels of urinary Cd, the body burden of Cd is assumed to be high as the results of long term exposure to Cd, especially in the time before our study was initiated. Irreversible renal damage is the consequence for these persons. On the other hand, some decreasing tendencies were observed among persons whose urinary B-m showed lower or about 1 mg/g.cr. These persons seem to have had much less exposure to Cd as they were relatively young and showed lower levels of urinary Cd. It will be interesting to know what factors relate to this decreasing tendency of urinary B-m including the decreasing tendencies of the Cd intake from rice, other crops or water in the younger persons.

In this follow-up study, we found one new occurrence of Itai-itai disease among the persons having a high level of B-microglobulinuria. Large fluctuations of urinary albumin were also observed according to the increasing tendency of urinary B-m. Further detail studies will be necessary to clarify this significance of albumin excretion into the urine. In this case, dramatic changes of the calcium metabolism were found. That is, after her suffering lumbago and lower extremity pain in 1979, serum levels of calcium decreased severely as well as phosphorus. As calcium in serum is very strictly regulated under normal conditions, this change rarely occurs except when nutritional deficiency is persist or cadmium

intoxication.

By roentgenological findings of the bone changes, typical characteristics of the osteomalacia such as looser's zone were found in 1986. As osteomalacia rarely occurs in adulthood, we can assume that her living in the polluted area and her consuming its agricultural products lead her to be suffering with Itai-itai disease, as well renal tubular dysfunction. As there are many persons within the area who have renal tubular dysfunction and who still continue to consume contaminated rice and other crops, it is very possible that other new cases of the Itai-itai disease will develop. Avoidance of consuming contaminated rice and other crops will be of vital importance. As well continual efforts must be made in further studies among those people still living in this whole area and in order to improve the environment.

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