Recent epidemiological studies on itai-itai disease as a chronic cadmium poisoning in Japan

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Abstract: Itai-itai disease is a chronic cadmium poisoning with renal tubular dysfunction followed by osteomalacia. Renal tubular dysfunction among inhabitants of the cadmium-polluted Jinzu River basin was irreversible and progressive, despite the fact that cadmium exposure had decreased. The bone mass was decreased in the inhabitants living in cadmium-polluted areas with renal tubular dysfunction, correlating with the urinary $\beta_2$-microglobulin level. The decreased bone mass was diagnosed as latent renal tubular osteomalacia. Low serum erythropoietin levels were detected among the patients with itai-itai disease, despite the presence of severe anemia. The anemia found in the end-stage of the disease was closely associated with an impaired renal function. Health surveys in cadmium-polluted areas of 8 prefectures were carried out, and many cases of renal tubular dysfunction were found in 4 prefectures, although the most severe cases were found in Toyama Prefecture. Many cases whose clinical features are completely in accord with those of itai-itai disease with severe renal tubular dysfunction and osteomalacia were reported in 3 prefectures as well as Toyama Prefecture. Mortality risks were increased in the patients with itai-itai disease, in the group suspected of having the disease, and in the groups of mild renal tubular dysfunction with 300–<1,000 µg/g creatinine. The development stage of the disease was divided into three stages. Those are the mild stage (stage of cadmium nephropathy) with the renal tubular dysfunction and decreased bone mass, the typical stage with the severe renal tubular dysfunction and pseudo-fracture detectable by X-ray examination, and the serious stage with severe renal dysfunction and pseudo-fracture and/or fracture.

Keywords: Chronic cadmium poisoning; itai-itai disease; mortality risk; osteomalacia; renal tubular dysfunction

Findings of itai-itai disease and the etiology

Onset of itai-itai disease

The Jinzu River basin in Toyama Prefecture is polluted by cadmium contained in a slag from a mine, located about 30 km upstream from the Toyama Plain, also paddy field soil and rice is contaminated by the metals. A disease characterized by severe pain appeared mainly among women in the 1920s, and health surveys were performed from after the end of World War II by a few researchers.

Dr. Noboru Hagino returning from the war in 1946, started the private clinic that was opened in the middle of the polluted areas by his father. He immediately found a curious disease. The disease attacked mostly elderly women and the pain first occurred in the lumbar area, shoulders, extremities and then the entire body. The patient gradually began to suffer from walking disturbances and after many years, it became difficult to move. At this stage bones were fractured from even the slightest pressure or force and so the patient groaned with severe pain. The patient gradually lost weight and wasted away and died. Dr. Hagino named the disease as itai-itai disease because the patients cried itai itai (ouch ouch). He started an epidemiological study, plotting all the locations of the patients he diagnosed and treated on a map. He found that all the patients were strictly distributed in the areas irrigated by the water of the Jinzu River.
Cadmium etiology of itai-itai disease

Cadmium was detected by Dr. Kobayashi in water from the Jinzu River, rice, and many organs from the patients of itai-itai disease. Many epidemiological studies were performed thereafter, and the largest scaled study was carried out by Toyama Prefecture (the Ministry of Health and Welfare and the Ministry of Education), supported by researchers from the Faculty of Medicine, Kanazawa University in 1963 to 1965. The patients were found among the inhabitants living in the Jinzu River basin only, and a high level of cadmium was detected in the urine of the patients and in the household rice. The concentration of cadmium was higher in the upper layer of soil and the inlet part of the paddy field, showing that cadmium was carried about by the irrigation. Almost all the patients were farmers and their life styles were the same as those of other control areas.

Many epidemiological studies in cooperation between Sweden and Japan were carried out, and they surveyed the length of residence in the area, the use of contaminated river water, and measured cadmium in household rice, urine, and blood. A correlation between cadmium exposure and renal tubular dysfunction indicated by the excretion of urinary $\beta_2$-microglobulin was shown (Kjellström et al., 1977; Shiroishi et al., 1977; Kojima et al., 1977). Friberg et al. (1971, 1974, 1985), concluded that the itai-itai disease was an expression of chronic cadmium poisoning, after evaluating all the data concerning the itai-itai disease in Toyama.

Countermeasures

The countermeasures by the Japanese government

Based on the epidemiological findings, the Ministry of Health and Welfare of Japan declared an official view on the etiology of itai-itai disease in 1968. Renal disorder is first caused by the chronic poisoning of cadmium, followed by the development of osteomalacia, which combines with inductive factors such as pregnancy, lactation, endocrinological irregularity, senility and calcium-deficient nutrition to result in itai-itai disease. The Jinzu River basin was designated in 1969, as an area to which the Relief Law (later taken over by the Compensation Law in 1974) should be applied. In 1972, the chief of the Environmental Pollution and Health Division of the Planning and Coordination Bureau of the Environmental Agency issued the recognition of four criteria defining itai-itai disease. (i) The patient should have been residing in an area heavily contaminated by cadmium, and should have been exposed to cadmium. (ii) The following findings in conditions (iii) and (iv) should not be congenital, and should have developed after one’s prime (mainly after menopause). (iii) Disorders in renal tubules should be observed. (iv) Findings of osteomalacia accompanied with osteoporosis should be evident from X-ray examinations or the biopsy of bones. If the fourth condition is lacking, the person should be authorized as a suspected patient and be under observation, because the possibility of the development of typical itai-itai disease can not be ruled out.

The compensation of victims

The written pledges to compensate victims were to compensate sufferers of itai-itai disease as well as those who are under medical observation and are suspected of having the disease, including those who will be diagnosed at a future time. By January 1999, the accumulated total number of patients identified as having itai-itai disease from 1967 were 180 women and three men. Only nine women and no men were still alive at that time. Those who registered as requiring observation were 97 women and 17 men and of these, four women and one man were still alive. Those who were once registered as requiring observation but later released from the registration were 114 women and 29 men and of these, 18 women and two men were still alive.
The compensation for contaminated paddy field soil
Toyama Prefecture investigated the area irrigated by the Jinzu River and of these 3,130 hectares (ha), designated an area of 1,500.6 ha as an agriculture area subject to soil pollution countermeasures by 1977. Cadmium concentration in brown rice harvested from the area was 1 ppm or more, or it seemed to exceed 1 ppm in all probability. The methods of “soil dressing after burying the polluted top soil” or “soil dressing directly onto the polluted top soil” were used. The restoration work started in 1980 from the upstream area. The work is still continuing and is expected to be completed in 2004. The cost of soil restoration for the primary area (90 ha; from 1979 to 1984) was about 2.4 billion yen with the polluter company paying 35.15%, and that for the second area (357 ha; from 1983 to 1994) was about 10 billion yen with the company paying 39.39%. The tertiary area (437 ha; from 1992 to 2004) is planned to cost about 21 billion yen and the polluter will bear 39.39%. The average cadmium concentration in brown rice harvested from the restored paddy fields and of the soil itself were 0.09 ppm and 0.16 ppm respectively (that from non-polluted paddy fields; 0.15 ppm), where the concentrations before restoration were 0.99 ppm and 1.12 ppm, respectively. Due to these results, an area of 646 ha (43% of 1,500.6 ha) was released from the designated status by 1997.

Epidemiological findings
Renal effects
Cadmium mainly attacks the kidney, and renal tubular dysfunction is brought about, characterized by the decrease of the reabsorption of many substances from tubule. The cadmium-induced renal tubular dysfunction produces the excess renal excretion of glucose, amino acids, minerals (such as calcium, phosphate, sodium, and chloride), and low molecular weight proteins (such as β2-microglobulin, lysozyme, retinol binding protein, vitamin D binding protein, and so on). The urinary activity of NAG (N-acetyl-β-D-glucosaminidase) was found in the urine of patients and suspected patients suggesting damaged epithelial cells of the renal tubule (Nogawa et al., 1983). The urinary activity of trehalase, specifically localized in tubular brush borders, also correlated with the increase of urinary β2-microglobulin suggesting damaged epithelial cells (Nakano et al., 1986; Nakano et al., 1987a; Nakano et al., 1987b; Iwata et al., 1988).

The important problem was the reversibility of renal tubular dysfunction. Renal tubular dysfunction was never reversed and some cases changed for the worse (Kubota, 1986; Kasuya et al., 1986; Teranishi et al., 1992). Recovered cases were found only in the group with low excretion of β2-microglobulin (less than 1000 µg/g creatinine). A follow-up study on renal tubular dysfunction was carried out on 193 female inhabitants of 11 districts of the cadmium-polluted Jinzu River basin and 40 reference subjects living in two adjacent districts in 1994–1995 (Fan et al., 1998). They were 54 to 70 years old when the initial examination was conducted in 1983–1984. The average cadmium concentrations in polished rice consumed by the subjects in the 1994–1995 study (0.12 ppm in 1994, 0.14 ppm in 1995) were significantly lower than those in the 1983–1984 study (0.26 ppm in 1983, 0.29 ppm in 1984), because of the restoration work. The average cadmium concentrations in polished rice from the reference areas were 0.07 to 0.15 ppm. The average cadmium levels in urine in the follow-up study were also significantly lower than those in the initial study (Figure 1, A). However, the mean values for urinary excretion of β2-microglobulin (Figure 1, B) were significantly higher 11 years later, indicating the progression of renal tubular dysfunction. A further increase was observed in the prevalence of renal tubular dysfunction determined by urinary β2-microglobulin exceeding 10 mg/g creatinine and urinary glucose exceeding 150 mg/g creatinine, only among inhabitants of the polluted areas. Thirty one new cases of renal tubular dysfunction were observed in the study. These results shows that renal tubular dysfunction among inhabitants of the cadmium-polluted Jinzu River basin is irreversible.
and progressive, and many new cases of renal tubular dysfunction were also noted over a period of 11 years, despite the fact that cadmium exposure had decreased over these years. The male inhabitants living in the cadmium-polluted area of the Jinzu River basin, also showed irreversible and progressive renal tubular dysfunction, although the magnitude of cadmium intake from rice was remarkably reduced (Cai et al., 1999).

Bone effects

The bone mass expressed by the metacarpal index and the relative cortical thickness decreased in the inhabitants living in cadmium-polluted areas with renal tubular dysfunction, correlating with the urinary $\beta_2$-microglobulin level (Aoshima et al., 1988; Kido et al., 1989; Aoshima and Kasuya, 1993). The decrease was more significant in women than in men.

Aoshima et al. (1993) examined calcium, phosphorus and vitamin D metabolism in 21 male and 13 female subjects with renal tubular dysfunction in the cadmium-polluted Jinzu River basin. Multiple proximal renal tubular dysfunction was detected in all subjects showing increased fractional excretion of $\beta_2$-microglobulin and fractional excretion of urate, generalized aminoaciduria and renal glucosuria. Hypophosphatemia due to the reduced ability of the tubular reabsorption of phosphate was observed in 31% of females, whereas the level of serum calcium remained normal in all subjects despite the decreased reabsorption of calcium. A serum level of 1,25-dihydroxyvitamin-D was inversely related to creatinine clearance in both men and women. However, the values were normal or increased in the subjects of this study. Serum iPTH (intact parathyroid hormone) was slightly increased, whereas the levels of other hormones such as 25OHD, calcitonin, thyroxine (T4) and triiodothyronine (T3) were normal. The serum alkaline phosphatase activity and serum osteocalcin concentration were significantly higher in both sexes. Bone loss was prominent in female subjects. It was concluded that itai-itai disease was cadmium-induced renal tubular osteomalacia. This conclusion was based on the findings of hypophosphatemia due to excessive renal phosphate excretion, increased urinary excretion of calcium, raised levels of bone alkaline phosphates and osteocalcin. The inhabitants living in the polluted area showing decreased bone mass should be diagnosed as having latent renal tubular osteomalacia.

Figure 1. The urinary level of cadmium [A] and $\beta_2$-microglobulin [B] in the initial study (1983–1984) and in the follow-up study (1994–1995), in 11 districts from cadmium-polluted areas and 2 districts from reference areas; female. The oblique lines indicate identical levels in both studies. In spite of the decrease of cadmium in the body, renal tubular dysfunction continued to increase for the next 11 years. (From Fan et al., 1998)
Blood effects

One of the important clinical features of itai-itai disease is severe anemia, appearing at the advanced stage of the disease with severe renal tubular dysfunction. Horiguchi et al. (1994) studied serum iron levels, serum erythropoietin, bone marrow morphology, and so on, to clarify the pathogenesis of the anemia, on ten patients with itai-itai disease. Low serum iron or ferritin levels were not observed, and bone marrow aspiration did not reveal any specific hematological disorders. A close relationship was observed between the decrease in the hemoglobin level and the progression of renal tubular dysfunction. Low serum erythropoietin levels were detected despite the presence of severe anemia. These results suggested renal damage plays an important role in the anemia which develops in itai-itai disease.

Renal tubular dysfunction and itai-itai disease in other cadmium-polluted areas apart from Toyama Prefecture

As described above, renal tubular dysfunction precedes the appearance of osteomalacia. The Japan Public Health Association Cadmium Research Committee (1989), supported by The Environment Agency, carried out health surveys in the cadmium-polluted areas of 8 prefectures in Japan, between 1976 and 1984, and reported that many cases of renal tubular dysfunction were found in Toyama, Ishikawa, Hyogo, and Nagasaki prefectures. Among the 426 participants of the tertiary screenings in the cadmium-polluted areas, about 200 cases were determined to have proximal renal tubular dysfunction and 116 of them were considered to require guidance from a physician because of the severity. X-ray examinations were performed on the participants of the tertiary screenings and bone atrophy was found in 108 cases out of 194 women participants and 57 out of 136 men from polluted areas of Toyama Prefecture. Only two cases were found in one woman and one man from the other seven prefectures. Compression fracture was also found in 40 women and 19 men living in polluted areas in Toyama, whereas the total of the other seven prefectures were two women and zero men.

Only the patients with chronic cadmium poisoning living in the Jinzu River basin are defined as itai-itai disease patients, because the Jinzu River basin was the only area to which the Relief Law applied. However, many cases whose clinical features are completely in accordance with those of itai-itai disease with severe renal tubular dysfunction and osteomalacia were reported in the cadmium-polluted areas in Japan. Nine cases of osteomalacia out of 11 cases of renal tubular dysfunction were reported in Tsushima, Nagasaki Prefecture (Saito et al., 1993). Two cases of osteomalacia diagnosed by pathological examination were reported in the Kakehasi River basin, Ishikawa Prefecture (Kido et al. 1991; Nakagawa et al., 1993a). Furthermore, 1 case very similar to itai-itai disease was found in the Totori River basin, Ishikawa Prefecture (Kitagawa, 1989). Five cases with renal tubular dysfunction and osteomalacia were found near the Ichi River, Hyogo Prefecture (Nogawa et al., 1975; Kitagawa, 1997).

The effect on survival time

In the early stage of investigation on itai-itai disease, it was considered that the life-span of the patients and suspected patients was not so different from that of the other inhabitants living in referenced areas. However, the long-term follow-up studies show the difference clearly. Kawano et al., (1986) carried out a follow-up study from April 1967 to October 1982 on 117 patients with itai-itai disease. The number of deaths during this period was significantly higher in the patients than in the controls. The mean survival time in the years up to October 1982 was 76.4 in the patient group and 78.3 in the control group (statistically significant). Nakagawa et al. (1990) conducted a follow-up study between 1967 to 1987 for patients diagnosed as having itai-itai disease, subjects who were suspected of having the...
They found that the cumulative survival rate of the subjects who were suspected of having itai-itai disease and who had severe renal dysfunction due to cadmium pollution was significantly lower than that of the control group.

They further studied the relationship between urinary β2-microglobulin and mortality in the cadmium-polluted Kakehashi River basin in Ishikawa Prefecture (Nakagawa et al., 1993b, 1996). Nakagawa et al. (1993b) showed that a tendency for increased mortality risk was found even with a relatively low level of renal tubular dysfunction, using the proportional Hazard Model of Cox. In females, an increased mortality risk was found as urinary β2-microglobulin concentrations increased, i.e., hazard ratios (ratios of mortality risk) of 1.58, 2.04, and 2.43 were found in the groups with 300–<1,000, 1,000–<10,000, and ≥10,000 µg/g creatinine, respectively, compared with the <300 µg/g creatinine group (Figure 2).

**Mechanism and development stages on itai-itai disease**

**Mechanism of itai-itai disease**

Figure 3 shows the main adverse effect of cadmium. Itai-itai disease is defined as cadmium-induced renal tubular osteomalacia. The direct effects of cadmium on bones, intestines, and others are not shown in this figure. Absorbed cadmium damages proximal renal tubule and
brings about the decreased reabsorption of many substances. Hypophosphatemia due to excessive renal phosphate excretion, over a length of time, causes osteomalacia. Pseudofracture, fracture, deformation of spine, and severe bone pain are the symptoms of osteomalacia.

**Development stages of itai-itai disease**

The development stages of itai-itai disease are summarized in Figure 4. Itai-itai disease is a chronic cadmium poisoning with renal tubular dysfunction resulting in osteomalacia, and it can be divided into three stages. Those are the mild stage (stage of cadmium nephropathy) with the renal tubular dysfunction and decrease of bone mass, the typical stage with the severe renal tubular dysfunction and pseudofracture detectable by X-ray examination, and the serious stage with severe renal dysfunction and pseudofracture and/or fracture.

A disease exactly the same as itai-itai disease found in Toyama Prefecture has not been reported from any other countries. However, many other countries have environmental cadmium pollutions. It is important to prevent the occurrence of itai-itai disease in the other countries in the future. It is also necessary to study the health effects of low level cadmium exposure.

**References**


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