Renal Research

Clinical and Experimental Contributions from Japan

Volume Editors
K. Kobayashi; K. Maeda, and K. Ohta, Nagoya

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Cadmium-Induced Proximal Tubular Dysfunction in a Cadmium-Polluted Area

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Introduction

Environmental cadmium pollution found in Japan, since it was believed to be playing a significant role in the development of so-called 'Itai-Itai disease' in the area around the Jinzu river, Toyama Prefecture, has now become a nation's major social and political problem (1, 2).

The present authors conducted health examinations on people in the highly cadmium-polluted Hosogoe area, Kosaka Town, Akita Prefecture, and discovered that many of them were suffering from proximal tubular dysfunctions – chronic cadmium poisoning – induced by environmental cadmium pollution.

This is the first report of the results of detailed renal function tests performed in a population living in a cadmium-polluted area.

Materials and Methods

The Hosogoe area of Kosaka Town is adjacent to a leading Japanese copper refinery that initiated operation in the 1870s. The soil of the area has been so significantly polluted by cadmium from industrial smokestacks that high concentrations of cadmium were detected at each test in the area's soil, rice, and vegetables. In 77 samples of unpolished rice produced in the area from 1970 to 1975, the mean concentration of cadmium (mean ± SD) was 0.66 ± 0.72 μg/g wet weight, some ten times as high as the corresponding level for the counterparts in non-polluted areas (1, 2).

Our examinations were carried out annually for four years from 1972 to 1975 on the residents of the area aged over 35 years. The target population for the four years totaled 152 (70 males and 82 females) in 73 households, mostly

Table I. Laboratory findings in 13 hospitalized cases with concurrent proteinuria and glucosuria

Case	Sex	Age	Years of residence	Urine								Plasma				
				RBP	β_2-microglobulin mg/g cr.	tubular proteinuria	GAA	minimum pH	maximum osmolality mOsm/kg·H_2O	culture	sediment	CR mg/dl	UA mg/dl	FBS mg/dl	Ca mg/dl	P mg/dl
1	M	66	46	(+)	12.6	(+)	(+)	5.28	692	negative	n.p.	1.5	2.8	79	10.2	2.6
2	M	65	50			(+)	(±)	5.24	804		n.p.	1.1	4.3	78	9.2	3.1
3	M	54	28	(−)		(+)	(+)	5.17	864	negative	n.p.	1.1	4.4	76	9.3	3.3
4	F	74	62			(+)	(+)	5.87	678	negative	n.p.	1.1	3.7	65	8.5	3.1
5	F	73	61	(+)	17.6	(+)	(+)	5.76	887	negative	n.p.	1.2	2.9	74	9.3	2.5
6	F	67	61			(+)	(−)	5.74	585	negative	n.p.	1.2	4.1	74	9.0	3.4
7	M	69	69	(+)		(+)	(−)	5.23	530		n.p.	1.7	3.3	67	9.1	3.6
8	M	67	67			(−)	(−)	5.04	674		n.p.	1.2	5.3	66	8.9	3.4
9	M	64	46		0.4	(−)	(−)	5.17	768		n.p.	1.3	4.3	59	8.8	2.6
10	F	68	55		0.2	(−)	(−)	5.04	701	negative	massive pus cells	1.3	4.3	90	8.3	3.6
11	F	60	47	(−)		(−)	(−)	5.00	803	negative	n.p.	0.9	3.7	66	8.7	4.4
12	F	58	47	(−)	0.3	(−)	(−)	5.13	770	negative	n.p.	0.8	4.7	63	9.5	4.4
13	F	53	37	(−)	0.1	(−)	(−)	5.07	836	negative	n.p.	0.7	4.9	86	9.8	4.1

RBP(+) = Retinol-binding protein more than 0.4 mg/dl; β_2-microglobulin = concentration in morning urine (mg/g creatinine); tubular proteinuria = analyzed by polyacrylamide gel electrophoresis; GAA = generalized aminoaciduria analyzed by thin-layer chromatography; minimum pH = values after acid loading test; maximum osmolality = values after overnight fasting; CR = creatinine; UA = uric acid; FBS = fasting blood sugar.

farmers, of which 147 people received our health examinations during the period.

Qualitative analysis was performed in morning urine employing 20 % sulfosalicylic acid test and Testape test. Concentrated urine proteins were analyzed by polyacrylamide gel electrophoresis (3), and urinary amino acids by thin-layer chromatography. Urinary retinol-binding protein was determined by counter immunoelectrophoresis, and urinary β_2-microglobulin by the radioimmunoassay method using ^{125}I (Pharmacia, Sweden).

Renal plasma flow was determined by PAH clearance, and the glomerular filtration rate by endogenous creatinine clearance. Phosphate clearance was measured by Fiske-SubbaRow's method, and uric acid clearance by the uric acid method. For the determination of bicarbonate threshold and of acidifying ability of urine, we used the oral bicarbonate loading test (4) and the ammonium chloride loading test, respectively.

Diagnosis of multiple proximal tubular dysfunctions was specifically established for the cases with either of the following two indications: (1) Completely satisfying 'phospho-gluco-aminoaciduria'. (2) Showing more than 4 of the following 6 indications, necessarily including renal glucosuria or generalized aminoaciduria – renal glucosuria; generalized aminoaciduria; decreased %TRP; high value of uric acid clearance; decreased HCO_3^--threshold; tubular proteinuria (3).

Results

1) Qualitative urine test: In the qualitative urine test performed five times during the four years, concurrent proteinuria and glucosuria was confirmed each time in 13–22 % of the tested subjects. There was no sex difference in the incidence.

Of 147 subjects examined (65 males and 82 females), 33 (18 males and 15 females) showed concurrent proteinuria and glucosuria. They contained 16 inmates in 8 households, comprising 4 husbands and wives (2 couples), 6 of parents- and children-in-law in 3 families, and 6 of blood parents and children in 3 families. There was a larger proportion of the affected with no blood ties.

2) Polyacrylamide gel electrophoretic analysis of urine proteins (tables I, II): Analysis for proteins was performed in 19 of the 33 cases with concurrent proteinuria and glucosuria. Tubular proteinuria was found in 10 of them, including 9 with multiple proximal tubular dysfunctions. On the other hand, 9 cases showing no tubular proteinuria included none with multiple proximal tubular dysfunctions.

3) Analysis of urinary amino acids by thin-layer chromatography (tables I, II): Analysis was performed in 25 of the 33 cases with concurrent proteinuria and glucosuria. Generalized aminoaciduria was identified in 7 of them, and a

Table II. Laboratory findings on 14 non-hospitalized cases with concurrent proteinuria and glucosuria

Case	Sex	Age	Years of residence	Ccr ml/min/ 1.48 m²	Cua ml/min/ 1.48 m²	Cua/ Ccr	% TRP	Urine				Plasma				Cd in urine μg/liter	Cd in rice μg/g
								RBP	β_2-microglobulin mg/g cr.	tubular proteinuria	GAA	CR mg/dl	UA mg/dl	FBS mg/dl	P mg/dl		
14	M	83	63	32	6	0.19	55	(+)	10.3	(+)	(+)	1.5	4.9	80	2.1	17.3	
15	M	36	36	84	23	0.27	72	(+)	0.6		(±)	1.0	2.6	75	2.8		0.57
16	F	80	80	28	10	0.36	47	(+)	146.8	(+)	(+)	2.1	2.9	76	2.0	15.3	0.50
17	F	73	57	22	8	0.36	78	(+)	48.5	(+)	(+)	1.7	3.0	94	2.7	12.6	3.86
18	M	83	81	43	13	0.30	68	(−)	4.7			1.2	3.3	90	2.7	13.8	1.26
19	M	56	56	42	4	0.11	89	(−)	0.5		(−)	1.1	5.0	55	2.7	11.3	
20	M	47	47	81	17	0.20	86	(−)			(−)	0.9	3.4	87	4.0		
21	M	43	43	103			89			(−)	(−)	1.0			3.0		0.67
22	M	42	42	80			86		0.1	(−)	(−)	1.0			3.1		0.64
23	M	35	35	73	9	0.12	86	(−)	0.1		(−)	1.0	3.4	68	4.0		
24	M	35	35	40	5	0.12	81	(−)	0.1		(−)	1.2	5.4	77	3.0		
25	F	80	53	57	17	0.30	83	(+)	7.7			0.9	2.6	98	2.4	13.7	1.26
26	F	61	61	146	47	0.32	82	(−)	5.2		(−)	0.8	2.1	75	2.8	11.7	
27	F	59	43	68	19	0.28	85	(−)	6.7	(±)	(±)	1.1	3.3	66	3.6		

Normal ranges: Cua/Ccr = 0.05–0.15; %TRP = 80–95; plasma uric acid = 3.8–7.5 mg/dl (adult males), 3.0–5.5 mg/dl (adult females); plasma phosphate = 2.8–4.3 mg/dl.

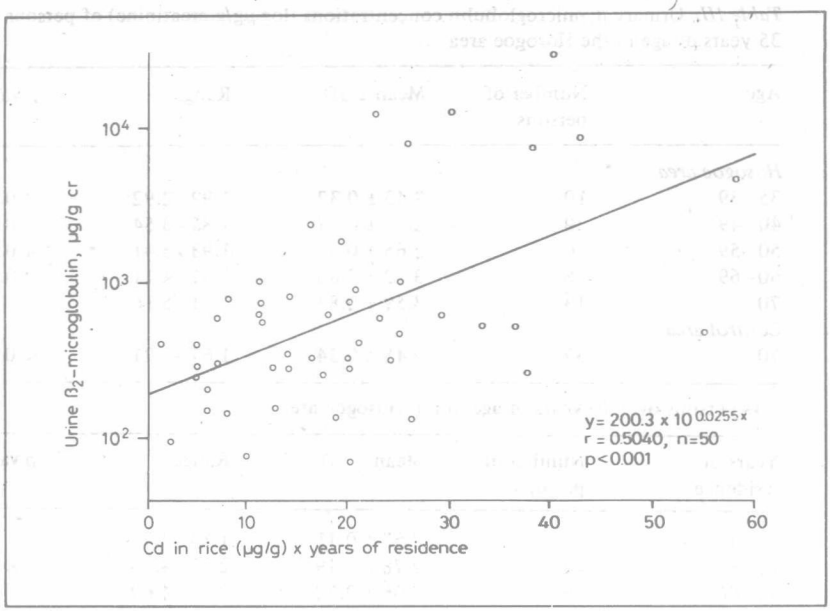

Fig. 1. Relationship between total body burden of cadmium (cadmium concentration in the residents' own produced rice multiplied by their resident years) and urinary β_2-microglobulin concentration in 50 residents over 35 years of age in the Hosogoe area.

slight increase in excretion of urinary amino acids in 3 cases. The remaining 15 cases were normal. All of the 7 cases showing generalized aminoaciduria and 2 of the 3 cases with a slight increase in excretion of urinary amino acids were diagnosed as having multiple proximal tubular dysfunctions. The same diagnosis was established in only one of the 15 normal cases in the analysis of urinary amino acids.

4) Urinary retinol-binding protein (tables I, II): This protein in morning urine was measured in 110 cases by counter immunoelectrophoresis. A level of over 0.4 mg/dl was identified in 11 of them, including 6 with multiple proximal tubular dysfunctions and 2 with some signs of proximal tubular dysfunctions. The other 3 remain untested. Only one out of 99 cases with a level of less than 0.4 mg/dl had multiple proximal tubular dysfunctions.

5) Urinary β_2-microglobulin (fig. 1, table III): In October 1975, β_2-microglobulin in morning urine was measured in 97 people (84 % of target population). People over 70 years of age showed a mean value of 3.59 ± 0.83 (ranging $2.51 \sim 5.16$) in urinary β_2-microglobulin concentration (log μg/g creatinine), while the corresponding figure in control people of the same age group in non-cadmium-polluted Ikawa Town, Akita Prefecture, was 2.48 ± 0.34 (ranging

Table III. Urinary β_2-microglobulin concentrations (log μg/g creatinine) of persons over 35 years of age in the Hosogoe area

Age	Number of persons	Mean ± SD	Range	p value*
Hosogoe area				
35–39	10	2.43 ± 0.37	1.92–2.92	< 0.001
40–49	30	2.61 ± 0.37	1.85–3.54	< 0.001
50–59	26	2.65 ± 0.39	1.93–3.41	< 0.001
60–69	18	3.02 ± 0.65	1.91–4.11	< 0.05
70–	13	3.59 ± 0.83	2.51–5.16	–
Control area				
70–	32	2.48 ± 0.34	1.67–3.21	< 0.001

* vs persons over 70 years of age in the Hosogoe area

Years of residence	Number of persons	Mean ± SD	Range	p value*
–40	41	2.63 ± 0.41	1.84–3.41	–
41–50	24	2.78 ± 0.49	2.03–4.10	n.s.
51–60	18	3.06 ± 0.78	2.03–4.69	< 0.01
61–	14	3.20 ± 0.83	2.22–5.16	< 0.001

* vs persons under 40 years of residence in the Hosogoe area

1.67 ~ 3.21), showing a statistically significant difference of the concentration between the two groups.

The urinary concentration of β_2-microglobulin in Hosogoe residents was found increasing with age. There was a statistically significant difference in mean urinary β_2-microglobulin concentrations between people from the 30s to 50s and the aged over 70 years. The people with longer residence in the area tended to show higher urinary β_2-microglobulin concentrations. There was a statistically significant difference in the mean concentrations between the residents for less than 40 years and those for more than 51 years.

Cadmium concentrations in the residents' own produced rice were measured for 50 of the 97 people who had urinary β_2-microglobulin levels determined. The value of cadmium concentration in unpolished rice of their production multiplied by their esident years had a close correlation with their concentration of urinary β_2-microglobulin ($y = 200.3 \times 10^{0.025x}$, $r = 0.5040$, $p < 0.001$).

6) Laboratory findings in 13 hospitalized cases with concurrent proteinuria and glucosuria (tables I, IV): 13 patients were hospitalized in the Tohoku University Hospital to receive detailed examinations. All were residents in Hosogoe, over 28 years, with no blood relation to each other. All cases revealed slight

Table IV. Laboratory findings on 13 hospitalized cases with concurrent proteinuria and glucosuria

Case	C_{PAH}	Ccr	Cua	Cua/Ccr	PSP test % 15 min	HCO_3^--threshold mEq/liter	% TRP	GTT	Plasma						Cd in urine μg/liter	Cd in rice μg/g
									Na mEq/liter	K mEq/liter	Cl mEq/liter	pH	pCO_2 mm Hg	CO_2-content mmol/liter		
1	490	46	25	0.54	25	27	67	normal	145	3.9	106	7.406	38.0	24.5	45.0	0.57
2		66	17	0.26	29		73	normal	140	4.7	106	7.400	39.0	24.7	19.0	0.68
3		82	10	0.12	28		77	normal	142	4.4	101	7.418	43.4	28.0		0.22
4	257	53	15	0.28	28	26	84	normal	143	3.2	107	7.362	42.7	25.3	3.4	0.42
5	268	57	19	0.33	32	23	70	normal	144	3.4	109	7.367	41.8	26.2	16.0	0.16
6		48	9	0.19	20	23	78	normal	141	3.6	110	7.376	40.0	24.1	6.3	0.98
7		48	13	0.27	22	26	85	normal	144	4.1	108	7.421	38.1	24.7	9.8	0.46
8	325	67	7	0.10	11		78	normal	148	4.2	106	7.410	39.8	26.2	15.1	2.44
9		64	11	0.17	33		85	normal	142	3.8	107	7.427	38.9	25.5	6.4	0.64
10	338	54	10	0.19	25	26	78	normal	142	4.2	103	7.380	44.8	26.7	10.5	1.27
11	524	59	12	0.20	33	25	82	normal	141	4.2	103	7.398	42.5	26.2	14.2	2.44
12	460	102	10	0.10	33	24	90	normal	144	3.7	107	7.390	40.3	24.5	13.1	0.68
13	497	78	8	0.10	20	24	87	normal	140	4.2	103	7.403	40.5	25.3	12.1	1.26

C_{PAH} = *p*-Aminohippuric acid clearance; Ccr = creatinine clearance; Cua = uric acid clearance (clearances in ml/min/1.48 m^2); 1.48 m^2 = body surface area of average Japanese adult; %TRP = renal tubular reabsorption of phosphate; GTT = oral 100 g glucose tolerance test; Cd in urine = cadmium concentration in morning urine; Cd in rice = cadmium concentration in unpolished rice of own production.

proteinuria ranging 20 ~ 100 mg/dl. With fasting blood sugar and glucose tolerance tests both normal, these patients were diagnosed as renal glucosuria cases. Most of them had endogenous creatinine clearance decreased to around 60 ml/min. In the uric acid clearance/creatinine clearance, 8 cases showed a high value of over 0.19. In %TRP, 7 cases showed an evident decrease of less than 79. In bicarbonate threshold, 4 cases had a decreased level of less than 24 mEq/liter, while reduced concentrating ability of urine was found in 8 cases.

Intravenous pyelography was carried out in all 13 patients. No abnormalities were detected in any case except patient 1 who had bilateral nephrolithiasis, patient 6 was one who had undergone right nephrectomy for nephrolithiasis at the age of 40. In blood gas analysis performed in all cases, none showed evidence of metabolic acidosis.

Physical and laboratory examinations performed in all cases revealed silicosis in patient 1, atrial fibrillation in patient 2, cirrhosis of the liver in patient 6, essential hypertension and chronic rheumatoid arthritis in patient 7, and chronic rheumatoid arthritis in patient 13. In the other 8 patients, no particular ailments were observed.

According to the diagnostic criteria described above, 6 (patients 1–6) of the 13 patients were diagnosed as having multiple proximal tubular dysfunctions.

7) Laboratory findings in 14 non-hospitalized cases with concurrent proteinuria and glucosuria (table II): Field-work renal examinations were performed in 14 patients, all being residents in the Hosogoe area for over 35 years. All the cases revealed glucosuria, which was determined as renal glucosuria on the basis of their fasting blood sugar in a normal range.

Two cases showed an elevated plasma creatinine concentration and a marked decrease in endogeneous creatinine clearance. In the uric acid clearance/creatinine clearance, 9 cases had a high value of over 0.19. Hypophosphatemia with a value of less than 2.7 mg/dl was found in 6 cases, and a low level of %TRP less than 79 was found in 5 cases.

On the basis of our described criteria, 4 (patients 14–17) of the 14 cases were diagnosed as having multiple proximal tubular dysfunctions. Detailed test results in the 13 hospitalized and 14 non-hospitalized patients have been reported elsewhere (5).

8) Bone X-ray findings: Bone X-ray tests were performed in all the 13 hospitalized and 5 of the 14 non-hospitalized patients (patients 14, 16, 17, 21, and 26), totaling 18 cases. All but patient 21 showed diffuse decreased bone density, the change more severe in females than in males. Spine formation of vertebral bodies was found in some males, and fish vertebrae or vertebral flattening in some females.

In the left pubic bone of patient 1, there was an indication suspected of Looser's line. No such sign was recognized in the other 17 cases. Bone biopsy was not carried out in these cases.

Discussion

Chronic occupational cadmium poisoning is well known as one of cadmium-induced health hazards.

Friberg first pointed out emphysema, anosmia and proteinuria as examples of health hazards characteristic to cadmium workers, further noting proteinuria as a symptom inevitable in long-engaged cadmium workers (6).

Subsequent clinical and experimental studies have made clear that chronic cadmium poisoning tends to accompany proteinuria, glucosuria, generalized aminoaciduria, decreased %TRP, hypouricemia and metabolic tubular acidosis (7–9). It is thus well established that renal lesions from cadmium poisoning are proximal tubular dysfunctions.

The present authors have found that 13 ~ 22 % of the Hosogoe residents (Kosaka Town, Akita Prefecture) over 35 years of age had concurrent proteinuria and glucosuria, showing their conspicuously high incidence of the lesion as compared with an average of about 2 % for the people in non-cadmium-polluted areas in Japan (2, 10). Of 147 residents in the Hosogoe area, 33 showed concurrent proteinuria and glucosuria. All of the 33 patients were in middle and old age, and had lived for a long time in the area. They showed some abnormalities associated with proximal tubular dysfunctions, such as a high concentration of urinary β_2-microglobulin, renal glucosuria, or a high value of uric acid clearance. In 10 of them, diagnosis of multiple proximal tubular dysfunctions was established. For identification of the lesion, electrophoretic analysis of urine proteins and analysis of urinary amino acids were recognized as highly reliable screening tests.

A variety of etiologic diseases are known with multiple proximal tubular dysfunctions (11). Six (patients 1–6) of the 10 patients with multiple proximal tubular dysfunctions were hospitalized for two months in the Tohoku University Hospital and received close examination. As a result, they showed no familial or hereditary diseases, nor any acquired diseases other than chronic heavy metal poisoning. Although thorough examinations were not carried out in the remaining 4 non-hospitalized patients (patients 14–17), they could be shown, on the basis of findings in their family history, past history, physical examination, blood chemical examinations, and urinalysis to have been associated with no other etiologic factors for multiple proximal tubular dysfunctions than chronic heavy metal poisoning.

The soil of their area has been so significantly polluted with cadmium that the agricultural products, such as rice and vegetables raised from the area, contain cadmium in abnormally high concentrations.

Residents of the area are mostly farmers and live on rice of their own production as staple food. Eventually, they must have been forced to take in cadmium in abnormally large amounts through their long-time intakes of rice and vegetables raised in the polluted soil.

Kojima in 1974 conducted extensive studies of 156 residents in 7 cadmium-polluted communities of Kosaka Town including Hosogoe, ages ranging 50–69 years (82 % of target population), and for 95 control people of the same age group (95 % of target population) in non-cadmium-polluted Ikawa Town, Akita Prefecture. Results are as follows: 58 of the 156 subjects in Kosaka Town revealed an extremely high concentration of urinary cadmium, over 10 μg/liter, in contrast with none in Ikawa Town showing such a level. The average urinary concentrations were 8.0 μg/liter for Kosaka residents but only 2.4 μg/liter for Ikawa residents, showing a statistically significant difference between the two. In daily cadmium excretion in feces, the mean value for 64 people in Ikawa Town was 50.5 μg/day, with none showing a value of over 150 μg/day, while that for 118 people in Kosaka Town was 176.8 μg/day, with over 150 μg/day in 50 % of them and over 300 μg/day in 16 % (10).

The rate of intestinal absorption of ingested cadmium is believed to be 5 % at largest. Then the daily excretion of cadmium in feces is almost equivalent to its daily intake (2). This clearly indicates that the people in Kosaka Town daily take in over three times as much cadmium as their counterparts in control areas.

Abnormally high concentrations of cadmium in rice of their own production and in urine of as many as 22 of 23 people with concurrent proteinuria and glucosuria verify that the residents now suffering from proximal tubular dysfunctions have been exposed to abnormally high levels of cadmium. The Kosaka residents' exposure to cadmium for many years and their development of proximal tubular dysfunctions substantially agree with the findings about chronic occupational cadmium poisoning and chronic experimental cadmium poisoning (6–9).

These findings have led the present authors to conclude that proximal tubular dysfunctions found in many of the residents of Hosogoe, Kosaka Town, Akita Prefecture is chronic cadmium poisoning induced by environmental cadmium pollution.

The concentration of urinary β_2-microglobulin in Hosogoe people were increasingly observed with age and resident years, indicating a significant difference from the corresponding trends in the control group.

β_2-Microglobulin, a kind of low molecular weight protein, is believed to increase in urine with defective reabsorption of proximal tubules (12).

It may be reasonable to believe that high levels of urinary β_2-microglobulin in Hosogoe residents have originated in proximal tubular dysfunctions existing in many of them. As the Hosogoe residents live mainly on rice of their own production, the value of 'the cadmium concentration in produced rice multiplied by resident years' can serve an excellent index of each individual's total body burden of cadmium. The residents' concentration of urinary β_2-microglobulin had a close correlation with this index, indicating a dose-response relationship

between an abnormally high level of urinary β_2-microglobulin, i.e. onset of proximal tubular dysfunctions, and the total body burden of cadmium.

The mean cadmium concentration in Hosogoe rice was 0.66 μg/g wet weight. The people habitually eating such rice for 51 years (index 33) will show a higher concentration than a mean + 2 SD (1,460 μg/g creatinine) for people in the control area. This estimation is justified by the variations in people's urinary β_2-microglobulin concentrations checked by resident years (fig. 1). The farmers habitually eating rice with 0.66 μg/g of cadmium concentration are believed to develop chronic cadmium poisoning in 50 years.

The best remedy against health hazards from environmental cadmium pollution is cessation of cadmium exposure with the improved environment.

It is highly desired that a drastic measure be enforced as soon and effectively as possible to restore the natural environment from the man-made pollution deplorably jeopardizing people's health.

Summary

Health examinations were performed in 147 people living in a cadmium-polluted area, Kosaka Town, Japan. 33 of 147 residents had some indications of proximal tubular dysfunction, such as renal glucosuria, tubular proteinuria, and aminoaciduria, and 10 of them were diagnosed as having multiple proximal tubular dysfunctions. Detailed examinations revealed that none of the cases had any causal diseases other than chronic cadmium poisoning. Residents' mean cadmium intake and mean urinary cadmium concentration were over 3 times as high as those in control areas. From these findings, renal lesions identified in these residents were concluded as chronic cadmium poisoning induced by environmental cadmium pollution.

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Hypertensive Changes in Experimental Nephritis Combined with Experimental Hypertension

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The mechanism of blood pressure elevation in glomerulonephritis seems to be variable, depending on its stages. It has been considered that hypervolemia appears to be a major contributor to hypertension in patients with chronic glomerulonephritis and near normal excretory function (1–4). In contrast to the stage without renal failure, renal humoral factors appear to contribute to the hypertensive process in chronic glomerulonephritis with reduced renal function.

Hypertension in chronic glomerulonephritis aggravates the clinical course of the disease, while the hypertensive type of chronic glomerulonephritis usually has a poor prognosis.

The present study was attempted to observe the interaction between nephritic and hypertensive processes in experimental nephritis and experimental hypertension in rats, and determine the role of hypertension in chronic glomerulonephritis.

Experiment I: Effect of Nephrotoxic Serum Nephritis on the Course of Experimental Renal Hypertension (Goldblatt's Type) in Rats

Methods

Female Wistar rats, weighing 180–200 g, were used for this experiment. During the entire study period, the rats were maintained on a diet of standard rat chow and tap water *ad libitum*. The rats were anesthetized with sodium amobarbital. A silver clip, 0.2 mm in width, was applied to the left renal artery

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