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OSSEOUS LESIONS OF THE HAND AND FOOT IN DIABETES MELLITUS: CORRELATION BETWEEN MAGNIFICATION ROENTGENOGRAPHIC FINDINGS AND CLINICAL FINDINGS

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ABSTRACT

Twofold magnification radiograms of hands and feet in 384 diabetic cases were reviewed to determine the correlation between clinical findings and osseous lesions, especially early changes. A small, well-demarcated, round radiolucent lesion (small lytic lesion) was the most frequent finding in 87.2% of the 384 patients. In particular, a small lytic lesion of less than 1 mm in diameter was encountered in 85.9% of all cases by magnification radiography. A small lytic lesion can be thought of not only as a specific finding but also as one of the prodromic findings of diabetic osteoarthropathy. Localized osteopenia was also specific for diabetes, with a fairly high frequency (39.1%). Multivariate analysis revealed significant correlation between osseous lesions, especially small lytic lesions, and retinopathy. Significant correlation between retinopathy and osseous lesions was also identified by clinical follow-up cases. These facts suggest that microangiopathy may play an important role in the development of osseous involvements.

Key words: Diabetes mellitus, Osteoarthropathy, Magnification radiography, Multivariate analysis

INTRODUCTION

Osseous abnormality is one of many complications of diabetes mellitus. Many reports on diabetic osteoarthropathy have been presented since Albright's first description (1). Most of them, however, dealt only with markedly destructive bone lesions. Although some papers (2, 6) referred to early osseous change, the correlation between roentgenographic findings and clinical findings was not discussed. In this paper, twofold magnification radiograms of hands and feet of diabetes mellitus patients are reviewed to determine the correlation between clinical findings and osseous lesions, especially early changes, and the pathogenesis of osseous disorders and the clinical role of magnification radiography of the bone in diabetes mellitus are discussed.

MATERIALS AND METHODS

From April 1981 to March 1984, 485 patients with diabetes mellitus were seen and treated at Chubu Rosai Hospital. We selected 384 of these 485 patients as our subjects and excluded the remaining 101 patients because they had renal dysfunction including proteinuria, or other disorders which could produce some effects upon the bone, such as liver cirrhosis or thyroid disease. Diagnosis of diabetes mellitus was based on the criteria prepared by the Japan Diabetic Society in 1970.

Of the 384 subjects, 190 were males with a mean age of 56.4 ± 12.4 years (ranging from 20 to

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83 years). Six of the 190 males were cases of insulin-dependent diabetes mellitus (IDDM), and 184 were cases of non-insulin dependent diabetes mellitus (NIDDM). There were 194 (7 IDDM cases and 187 NIDDM cases) female subjects with a mean age of 59.5 ± 11.1 years (ranging from 20 to 80 years). Duration of disease, fasting blood sugar value (FBS), and evaluation of results of glucose tolerance test (based on the criteria by the 3rd Department of Internal Medicine, Nagoya University School of Medicine) for each patient are shown in Table 1. Retinopathy was seen in 78 of the 190 (41.1%) males and in 102 of the 194 (52.6%) females. Neuropathy was found in 31 of the 190 (16.3%) males and in 33 of the 194 (17.0%) females. Fifty-two healthy control subjects were also studied, 32 of whom were males with a mean age of 57.0 ± 11.0 years (ranging from 35 to 75 years) and 20 of whom were females with a mean age of 53.0 ± 12.8 years (ranging from 33 to 78 years).

For magnification radiography, an apparatus with a 0.1-mm focal spot X-ray tube HITACHI DH-1512A) was used. The focus-object (center of thickness) distance was 80 cm and focus-film distance was 160 cm, giving a magnification ratio of 2.0. The exposure data were 54 - 58 kVp, 15 mA, 0.4 sec. Both hands and feet were radiographed in each subject.

Abnormal radiographic findings were classified into six groups as follows:

1) Small lytic lesion (X-1): A small, well-demarcated, round radiolucent lesion located mainly in the juxta-articular cortical bone in the phalanges. Small lytic lesions were subdivided into microlytic lesions (less than 1 mm) and macrolytic lesions (ranging from 1 to 4 mm). (Fig. 1).
2) Destructive lesion (X-2): A destructive osteolytic lesion with some deformity. One of classical, typical diabetic osteoarthropathy.
3) Osteopenia (X-3): Lesions with decreased density of the bone. They were subdivided into localized (Fig. 1, Fig. 2) and generalized osteopenia.
4) Sclerosis (X-4): Lesions with increased density of the bone.
5) Articular lesion (X-5): Narrowing or disappearance of the articular space, subluxation, and other articular changes.

Table 1. Clinical data in 384 cases of diabetes mellitus

A: Duration of disease

Duration (Years)	1 No.	2-5 No.	6-10 No.	11-15 No.	16-20 No.	20< No.	Mean Years
male	24	50	68	22	14	12	8.2
female	10	57	60	36	27	4	8.7
total	34	107	128	58	41	16	8.5

B: Fasting blood sugar (FBS)

FBS mg/dl	<140 No.	140-200 No.	200< No.	Mean mg/dl
male	115	55	20	136
female	106	66	22	144
total	221	121	42	140

C: Gulcose tolerance test (GTT) classification

	L No.	M No.	S No.
male	62	45	83
female	37	60	97
total	99	105	180

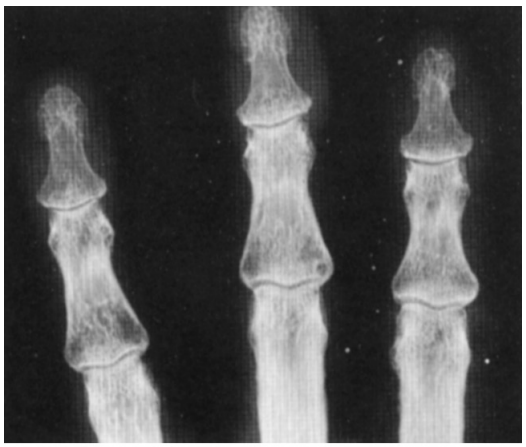

Fig. 1 Multiple small lytic lesions are seen in juxta-articular areas of the interphalangeal joints. Localized osteopenia is also revealed in the proximal area of each middle phalanx (Twofold magnification radiogram).

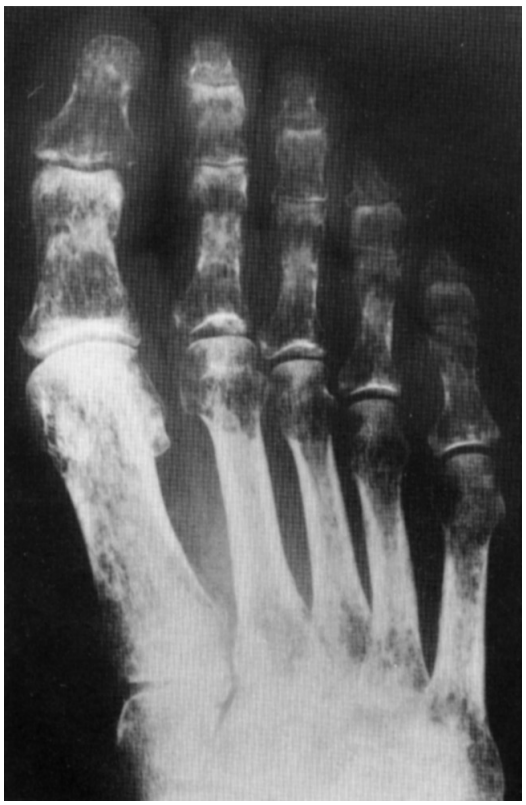

Fig. 2 Radiogram of the right foot shows multiple areas of mottled demineralization (localized osteopenia) with disuse osseous atrophy (Twofold magnification radiogram).

6) Vascular calcification (X-6): In addition to marked calcification, a fine and faint calcification on magnification radiogram was also included in this group.

The relations between the frequency of these roentgenographic findings and multiple clinical factors including sex, age, and clinical data were analyzed using multivariate analysis method with a microcomputer (Sharp MZ-80B) (12). Clinical data include duration of the disease, fasting blood sugar value (FBS), severity of disease, degree of obesity, serum calcium and serum triglyceride values, retinopathy, and neuropathy. At numerical analysis of each data, a mean value of fasting blood sugar values measured several times during one year before roentgenographic examination for FBS value, a mean value of one-hour and two-hour blood sugar values in glucose tolerance test for severity of disease, and Scott's classification for retinopathy were used. For neuropathy, neurological findings including the results of a fall in the motor nerve conduction velocity in 84 cases were taken into consideration with the results as follows: 0: no neuropathy; 1: slight neuropathy; and 2: severe neuropathy. For the remaining clinical data, measured values were used. At numerical analysis of roentgenographic findings except X-1, scores from 0 to 6 according to severity of bone involvement were assigned to each group of roentgenographic findings. For X-1, the lesions were measured and classified as follows: score 1: smaller than 1 mm; score 2: from 1 mm to 3 mm, score 3: larger than 3 mm; all scores were then summed up.

In cases followed up for more than two years, changes in findings were also reviewed.

RESULTS

Frequency of each roentgenographic finding in diabetics was shown in Table 2a. A small lytic lesion was the most frequent (87.2%) of the six findings. An especially high frequency was noted for microlytic lesions which were detected in 85.9% of the 384 patients. The frequency and mean score of small lytic lesions by age distribution increased with aging (Table 3a). In 44.2% of 52 control subjects, roentgenographic findings similar to this small lytic lesion were found (Table 2b). Although the frequency and mean score of roentgenogrpahic findings similar to a small lytic lesion increased with aging in the controls, both of them were much lower than those in the diabetic group (Table 3a, Table 3b). In addition, most of the roentgenographic

Table 2a. Frequency of each magnification roentgenogrpahic finding in diabetic hands and feet

roentgenographic finding	male (n=190) %	female (n=194) %	total (n=384) %
X - 1 small lytic lesion	87.4	87.1	87.2
(microlytic lesion	85.8	86.6	85.9)
(macrolytic lesion	32.1	28.4	30.2)
X - 2 destructive lesion	14.4	16.5	15.4
(erosion	12.6	15.5	14.1)
(bone disappearance	6.3	6.2	6.3)
(reconstruction	1.6	0.5	1.0)
X - 3 osteopenia	35.8	51.0	43.5
(localized lesion	34.7	43.3	39.1)
(generalized lesion	1.6	12.4	7.0)
X - 4 sclerosis	15.3	12.4	13.8
X - 5 articular lesion	8.4	16.0	12.2
X - 6 vascular calcification	52.1	59.3	55.7

Table 2b. Frequency of each magnification roentgenographic finding in hands and feet of control subjects

roentgenographic finding	male (n=32) %	female (n=20) %	total (n=52) %
X - 1 small lytic lesion	53.1	30.0	44.2
(microlytic lesion	50.0	30.0	42.3
(macrolytic lesion	3.1	5.0	3.8)
X - 3 osteopenia	3.1	5.0	3.8
(localized lesion	3.1	5.0	3.8)
(generalized lesion	0.0	0.0	0.0)
X - 5 articular lesion	0.0	5.0	1.9
X - 6 vascular calcification	3.1	10.0	5.8

Destructive lesion (X-2) and sclerosis (X-4) were not encountered.

Table 3a. Frequency and mean score of small lytic lesion by sex and age distribution in diabetic group

age	*male*			*female*		
	no. of cases	frequency %	mean score	no. of cases	frequency %	mean score
- 29	2	0.0	0.0	2	0.0	0.0
30 - 39	16	68.8	10.8	11	54.5	9.2
40 - 49	38	81.6	14.6	20	80.0	9.2
50 - 59	58	87.9	20.4	51	90.2	16.4
60 - 69	44	93.2	27.2	74	91.9	20.0
70 -	32	100.0	28.2	36	91.7	9.6
total	190	87.4	21.2	194	87.1	19.6

Table 3b. Frequency and mean score of small lytic lesion by sex and age distribution in control subjects

age	*male*			*female*		
	no. of cases	frequency %	mean score	no. of cases	frequency %	mean score
- 39	1	0.0	0.0	2	0.0	0.0
40 - 49	9	44.4	3.8	6	16.7	1.6
50 - 59	8	50.0	3.8	7	42.9	2.2
60 - 69	8	62.5	5.8	2	50.0	4.0
70 -	6	66.7	5.0	3	33.3	3.6
total	32	53.1	4.6	20	30.0	2.2

findings found in the controls that were similar to the pathological small lytic lesions were located near the distal interphalangeal joint, while pathological small lytic lesions found in the patients with diabetes mellitus were detected near the proximal interphalangeal joints and even near the metacarpo- and metatarso-phalangeal joints. In about 80% of the diabetic patients with small lytic lesions, the lesions were located even near the metacarpo- or metatarso-phalangeal joints. When the total score of small lytic lesions of both hands and feet in each diabetic patient was larger tan the total value which was added two times value of the standard deviation to the mean score of each age group in the healthy controls, this diabetic patient was assumed

Table 4. Corrected frequency of small lytic lesion by sex and age distribution in diabetic group

age	male %	female %	total %
- 29	0.0	0.0	0.0
30 - 39	56.3	45.5	51.9
40 - 49	60.5	30.0	50.0
50 - 59	55.2	52.9	54.1
60 - 69	77.2	68.9	72.0
70 -	84.4	88.9	86.8
total	65.8	62.4	64.1

to have abnormal small lytic lesion. The frequency of the abnormal small lytic lesions was then called the corrected frequency as shown in Table 4. Corrected small lytic lesion was also the most frequent of the six roentgenographic findings and had already appeared in over half of the patients in their 30s. There was no significant sex difference of the frequency of small lytic lesions by age distribution. However, these lesions were encountered more frequently in males in the 40-49 years-old age-group than in females of the same age group (Table 4).

Macrolytic lesion, vascular calcification, and localized osteopenia were found in 30.2%, 55.7%, and 39.1% of the 384 patients, respectively. Osteopenia was seen more frequently in females (51.0%) than in males (35.8%). Most of it was localized and scattered. The frequency of diffuse osteopenia was 1.6% in males and 12.4% in females.

Destructive lesion, sclerosis and articular lesion were found in 12.2% to 15.4% of all patients. Articular lesion was more frequent in females (16.0%) than in males (8.4%). About 80% of all patients showed at least one osseous lesion. Other roentgenographic findings, such as periosteal new bone formation, fracture (fragmentation), and soft tissue swelling with air bubbles, were seen in some cases.

In the control subjects, vascular calcifications were found in three cases, localized osteopenia in two cases, and an articular lesion in one case.

Twenty-one of the 384 patients were followed up for more than two years. Their osseous lesions progressed, did not change, or improved during this interval (Table 5, Fig. 3, 4, 5). Improvement was found in two cases with small lytic lesions and one of osteopenia. There was no significant relation between the change of osseous lesions and the clinical data, though a few cases showed a close relation between both factors (Fig. 5).

The results of correlation analysis were shown in Table 6. In males, there was a high correlation between age and all osseous lesions but sclerosis. Both small lytic lesions and osteopenia showed significant correlation with retinopathy and with neuropathy, and destructive lesions with retinopathy. In the female group, there was a significant correlation between age and all

Table 5. Changes in roentgenographic findings of 21 cases followed up for more than two years

	osteoarthropathy			*vascular calcification*		
	male (n = 9)	female (n = 12)	total (n = 21)	male (n = 9)	female (n = 12)	total (n = 21)
improved	1	2	3	1	0	1
unchanged	5	3	8	6	10	16
progressive	3	7	10	2	2	4

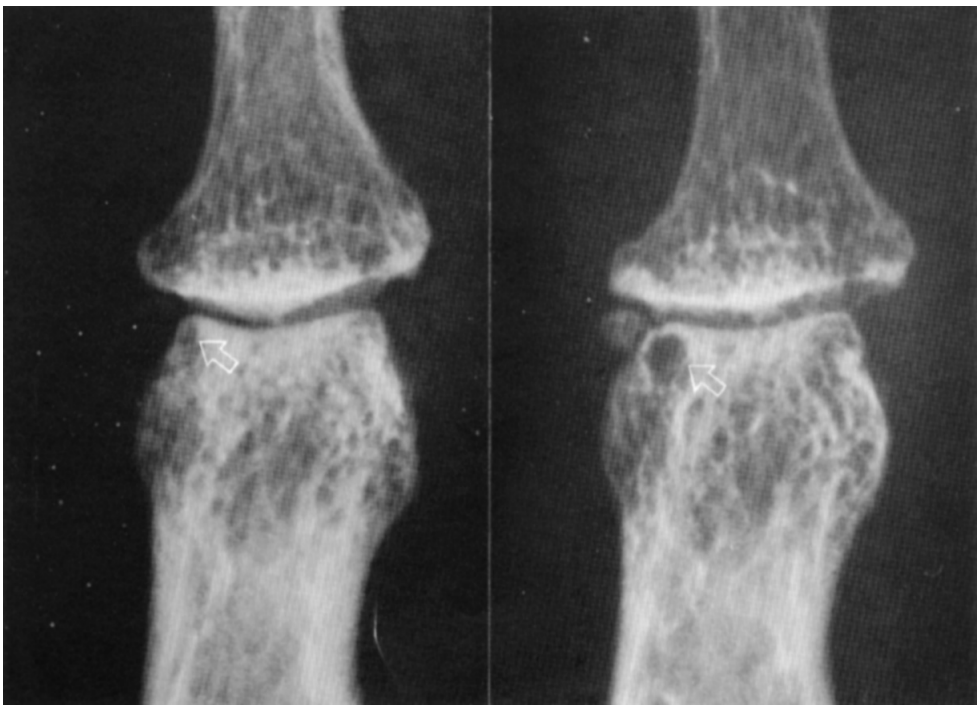

Fig. 3 A microlytic lesion with a diameter of 0.5 mm is seen in the distal end of the middle phalanx (3A: arrow). Eight months later, this lesion became enlarged to a diameter of 2 mm (3B: arrow) (Twofold magnification radiograms).

Table 6a. Correlation analysis between magnification roentgenographic findings and clinical findings in males

	X - 1	X - 2	X - 3	X - 4	X - 5
Age	0.485***	0.179*	0.323***	0.131	0.220**
Duration	0.196**	0.127	0.142*	0.020	0.087
FBS	−0.063	−0.057	0.011	0.083	−0.150
Severity	0.014	−0.018	−0.012	0.064	−0.130
Nutrition	0.148*	0.089	−0.079	0.025	0.061
S. Calcium	−0.098	−0.103	0.048	0.017	−0.011
Triglyceride	−0.003	−0.004	0.012	−0.041	−0.006
Retinopathy	0.217**	0.191*	0.257***	0.073	0.092
Neuropathy	0.151*	0.003	0.201**	−0.063	0.067
X - 6	0.055	0.084	0.218**	0.033	−0.008

X - 1 = small lytic lesion, X - 2 = destructive lesion, X - 3 = osteopenia, X - 4 = sclerosis, X - 5 = articular lesion, X - 6 = vascular calcification
* = $P<0.05$, ** = $P<0.01$, *** = $P<0.001$

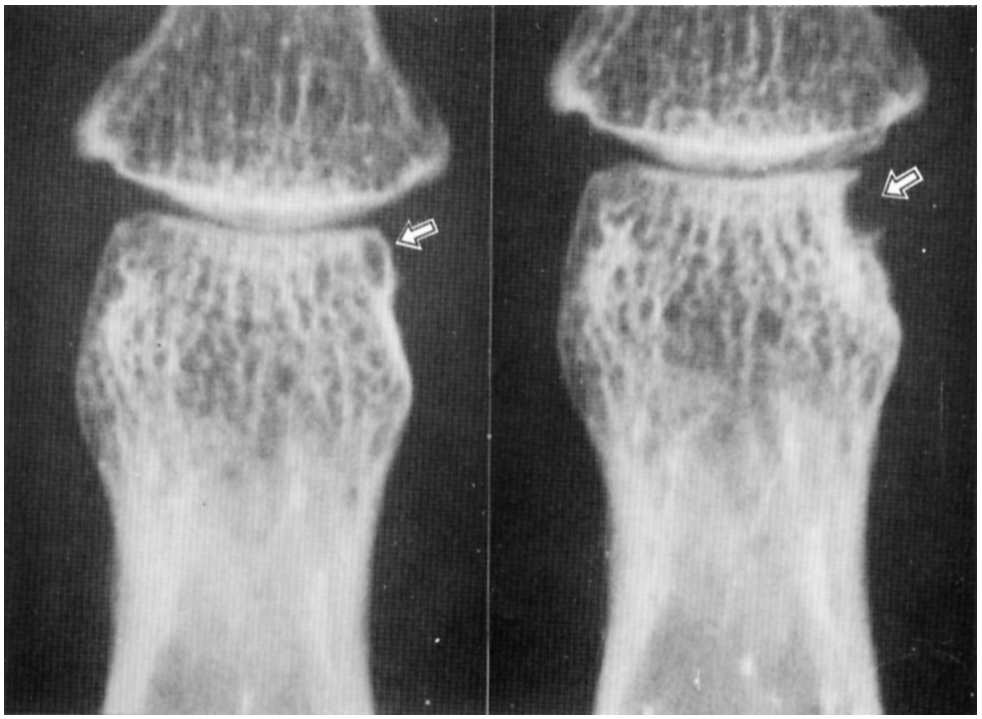

Fig. 4 A small lytic lesion wth sharp margin can be seen in the distal end of the middle phalanx (4A: arrow). Eighteen months later, this lesion progressed to an early destructive lesion (4B: arrow) (Twofold magnification radiograms).

Table 6b. correlation analysis between magnification roentgenographic findings and clinical findings in females

	X - 1	X - 2	X - 3	X - 4	X - 5
Age	0.507***	0.092	0.360***	−0.249**	0.244**
Duration	0.066	0.060	0.129	0.042	0.098
FBS	−0.020	−0.048	−0.130	0.043	−0.016
Severity	0.024	0.005	−0.047	0.054	0.075
Nutrition	0.038	−0.088	−0.136	−0.128	−0.158*
S. Calcium	0.110	−0.043	−0.027	−0.006	0.011
Triglyceride	0.161*	−0.050	0.035	−0.092	0.167*
Retinopathy	0.217**	0.225**	0.178*	0.134	0.158*
Neuropathy	0.077	0.283***	0.109	−0.030	0.174*
X - 6	0.210**	0.039	0.087	−0.048	−0.007

X - 1 = small lytic lesion, X - 2 = destructive lesion, X - 3 = osteopenia, X - 4 = sclerosis, X - 5 = articular lesion, X - 6 = vascular calcification
* = $P<0.05$, ** = $P<0.01$, *** = $P<0.001$

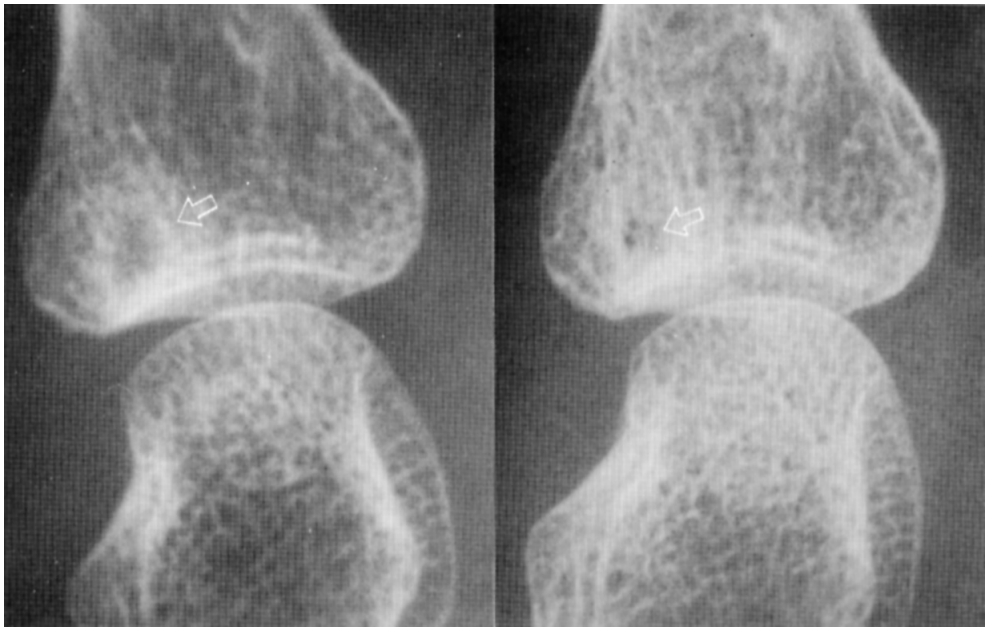

Fig. 5 A small lytic lesion with a diameter of 2 mm (5A: arrow) has improved two years after with reconstruction of osseous trabeculae (5B: arrow). Retinopathy has also improved during this periof from Scott's classification III to II (Twofold magnification radiograms).

osseous lesions but destructive lesions. All osseous lesions but sclerosis showed significant correlation with retinopathy. Destructive lesions correlated with neuropathy. There was no correlation with FBS, severity, and serum calcium in either the male or female groups.

Correlation between small lytic lesions and clinical data, including age, duration of the disease, FBS, serum calcium, triglyceride, retinopathy and neuropathy, analyzed by multiple regression analysis method, was significant. The multiple correlation coefficiency was 0.54 ($P < 0.005$) in males and 0.55 ($P < 0.005$) in females but neither value was satisfactory for clinical use. Correlation between other bone lesions and clinical findings was not significant because of low incidence of osseous lesions. Principal component analysis and discriminant analysis also showed no significance.

Although osseous lesions were detected more in the group of patients treated with oral agents than in that treated with insulin and diet, there was no significant correlation between osseous lesions and the method of therapy.

DISCUSSION

Small lytic lesion, especially microlytic lesion, was the most noteworthy roentgenographic finding in this study. A similar roentgenographic finding was seen in some of the control subjects with aging. However, small lytic lesions found in patients with diabetes mellitus are specific for the disease because of their high frequency rate in diabetes mellitus and because of their wide and multiple distribution even near the metacarpo- or metatarso-phalangeal joints. Their mechanism of development is probably due to some factor caused by diabetic disorders because pro-

gressive changes from microlytic lesion to destructive lesion were seen in our follow-up cases. Therefore, this small lytic lesion is one of the prodromic findings of diabetic osteoarthropathy.

Geoffroy *et al* (6) reported a similar roentgenographic finding corresponding to our small lytic lesion as geode. He found geode in 3.7% of 1501 patients. High frequency in our series is due to the effect of magnification radiography (13).

Localized osteopenia may also be specific for diabetes mellitus. Few reports but Pogonowska's (2) referred to this finding. Microangiopathy may play a part in formation of localized osteopenia as indicated by the significant correlation between them.

Vascular calcification is also found more frequently in our series compared with that of other reports (2, 3, 6). Magnification radiography is also useful for detecting a fine and faint calcification.

The above three roentgenographic findings and the other three findings, i.e. destructive lesion, sclerosis, and articular lesion, were detected scatteringly in their distribution without a given rule.

It is generally accepted that poorly controled patients with diabetes mellitus show various osseous lesions more frequently than well-treated patients (4. 7, 8). Sato *et al* (7) reported that the urinary excretion rate values of calcium correlated positively with the degree of hyperglycemia. The development of osteoporosis and its severity was found to be related to the duration of diabetes and to the degree of hypercalciuria by Rizivi (5). However, our results of correlation analysis of osseous lesions and clinical laboratory data, including fasting blood sugar, severity of diabetes mellitus, and serum calcium, showed no intimate relation. There was also no correlation with urine calcium value. Poor control of diabetes mellitus and hypocalcemia may not cause osseous lesions etiologically, although they may induce osseous lesions in acutely progressed cases. Significant correlation between osseous lesions, especially microlytic lesions, and retinopathy suggests that microangiopathy may play an important role in the development of osseous changes (2, 9). Thickening of the basement membrane in microangiopathy may interfere with nutrition of bone but not with the circulation of blood. Osteolysis does not result from ischemia because adequate blood supply is necessary in the development of osteolysis (2). Significant correlation between vascular calcification (macroangiopathy) and osteopenia in males or small lytic lesions in females in this series, however, suggests that macroangiopathy may also play some role in the occurrence of osteopathy in diabetes mellitus (14, 15).

Some authors (4, 10, 11) reported that peripheral neuropathy was etiologically related to the diabetic osteopathy. Although there was significant correlation in females between articular lesion and neuropathy, no finding of Charcot's joint could be found in this series; therefore, neuropathy can not be considered responsible for the diabetic osteopathy. Some common factors including microangiopathy may cause the diabetic osteopathy and neuropathy (16).

From the review of cases followed up for several years, diabetic osteopathy can be reversible in some well-controlled patients. Significant correlation between retinopathy and osseous lesions is identified by our two clinical cases. This findings also supports the intimate correlation between microangiopathy and osseous lesions.

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