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Ionized calcium and 1,25-dihydroxyvitamin D concentration in serum of patients with sarcoidosis

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Ionized calcium and 1,25-dihydroxyvitamin D concentration in serum of patients with sarcoidosis. K. Hamada, S. Nagai, T. Tsutsumi, T. Izumi. ©ERS Journals Ltd 1998.

ABSTRACT: The aim of this study was to evaluate alterations in calcium metabolism in sarcoidosis.

The serum concentrations of calcium (sCa), ionized calcium (sCa^{2+}), 1,25-dihydroxyvitamin D ($s1,25(OH)_2D_3$) and parathyroid hormone (sPTH), serum angiotensin-converting enzyme activity (sACE) and urinary excretion of calcium (uCa) were studied in 36 Japanese patients with pulmonary sarcoidosis, aged 48.1±15.3 yrs (mean±SD), 15 males and 21 females. During the study the patients were on a daily diet with 500 mg calcium and 1000 mg phosphorus for a total of 6 days.

sCa^{2+} was above the normal range (>1.26 mmol·L^{-1}) in 10 patients (27.8%), 12 patients (33.3%) were hypercalciuric, and 16 patients (44.4%) showed alteration in calcium metabolism, with an increase in values of sCa, sCa^{2+} or uCa. There was a significant correlation between sCa^{2+} and $s1,25(OH)_2D_3$ ($p<0.001$), as well as between sCa^{2+} and sACE ($p<0.001$). $s1,25(OH)_2D_3$ in patients with extrathoracic involvement (ETI) tended to be higher than in patients without ETI. sCa^{2+} was less than 1.23 mmol·L^{-1} ($p<0.05$) in the majority of patients without ETI, and sCa^{2+} was less than 1.24 mmol·L^{-1} in the majority of normocalciuric patients.

In conclusion, a disease-related alteration in calcium metabolism was seen in about 40% of patients with sarcoidosis, and 1,25-dihydroxyvitamin D probably plays a crucial role in this abnormality. The serum concentration of ionized calcium was considered to be a useful index for the disease activity of sarcoidosis.

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Serum ionized calcium, which constitutes 46–50% of serum calcium, is the only biologically active form of calcium. The serum concentration of ionized calcium (sCa^{2+}) is strictly regulated within a narrow range. For this reason, when evaluating calcium metabolism and interactions between calcium and vitamin D or between calcium and parathyroid hormone (PTH), sCa^{2+} could be a more reliable index than the serum concentration of calcium (sCa) or albumin-adjusted sCa (adjCa). 1,25-Dihydroxyvitamin D ($1,25(OH)_2D_3$), the most biologically active form of vitamin D, is usually produced within renal tubules. Because the ultimate aim of this process is to keep sCa^{2+} stable, the production of $1,25(OH)_2D_3$ in kidneys is strictly regulated by sCa^{2+}, serum concentration of (s)PTH, and the serum concentration of phosphorus [1].

At granuloma sites, $1,25(OH)_2D_3$ is produced by 25-hydroxyvitamin D-1α-hydroxylase within activated alveolar macrophages and epithelioid cells, which play crucial roles in granuloma formation [2–4]. This extrarenal production of $1,25(OH)_2D_3$, although not as tightly regulated as in the kidneys, occurs in a substrate-dependent manner [2, 5]. A portion of extrarenally produced $1,25(OH)_2D_3$, taken into systemic blood circulation, probably causes an excess of calcium transport at the small intestine and, at the same time, an excess of bone resorption, which is thought to bring on an imbalance of calcium, hypercalcaemia or hypercalciuria, in patients with sarcoidosis [6–11].

Since HARRELL and FISHER [12] suggested a positive correlation between vitamin D and hypercalcaemia in sarcoidosis for the first time in 1939 [12], a number of studies has been reported about the abnormal metabolism of calcium and vitamin D in patients with sarcoidosis. However, the significance of the correlation between sCa and $s1,25(OH)_2D_3$ is thus far controversial.

In the current report, sCa^{2+} was the point of focus instead of sCa. Whether or not sCa^{2+} reflects systemic extension of the disease and the disease activity was also studied by testing correlations with the activity of extrathoracic involvement (ETI) and hypercalciuria. Concerning an index for the disease activity of sarcoidosis, angiotensin-converting enzyme (sACE) has been one of the most reliable serum markers since LIEBERMAN *et al*. [13] reported its availability. However, it cannot be uniformly evaluated since the polymorphism of the gene was shown to affect sACE [14]. sACE still remains a useful index for disease activity, but alternative indices are needed that can reliably evaluate the activity of disease. In this respect an investigation was conducted into whether or not sCa^{2+} could reflect disease activity.

Methods

Materials

Thirty six sarcoidosis patients, consisting of 15 males and 21 females aged 48.1±15.3 yrs (mean±SD), were entered into the study (table 1). No entry criterion regarding disease duration was set in this study. The durations varied widely from 1–324 months, with three patients having been followed for >5 yrs, and five patients in >10 yrs. Six patients whose chest radiographs showed stage I or II sarcoidosis and presented elevated sACE and/or uveitis (the most frequent ETI among Japanese patients with sarcoidosis [15]), although not histologically proven, were clinically diagnosed with sarcoidosis. Histologically unproven patients whose chest radiograph did not show bilateral hilar lymphadenopathy (BHL) were excluded. Twenty eight patients had received no previous corticosteroid therapy, except for local use on ophthalmological or dermatological lesions, which was considered to have little systemic effect. Eight patients had previously had systemic corticosteroid therapy, but the treatment had been discontinued >1 yr before the study because of an improvement in symptoms. Patients who had received systemic corticosteroid therapy within 1 yr before the study were excluded. All patients had normal renal function except for two patients who had histories of nephrolithiasis and slightly reduced creatinine clearance. Patients were excluded if they had been diagnosed with hyperparathyroidism or hypoparathyroidism and primary bone diseases before the study. No primary or secondary endocinological disorders, except those due to sarcoidosis, were detected at the time of the study.

Table 1. – Profiles and radiographic data of 36 patients with sarcoidosis

Data	Number
Age yrs (mean±SD)	48.1±15.3
Males/females	15/21
Duration months (mean±SD)	51±69
Chest radiography stage*	
0	2
I	12
II	18
III	4
Diagnosis	
Transbronchial lung biopsy	19
Skin biopsy	5
Lymph node biopsy	5
Liver biopsy	1
Clinical+	6
Symptoms	
Asymptomatic	12
Symptomatic	24
Ocular	16
Respiratory	12
Febrile	2
Extrathoracic lesion	
Uveitis	20
Skin	10
Superficial lymph nodes	5
Kidney	1
Liver	1
History of nephrolithiasis	3
Treatment	
Untreated	28
Previous corticosteroid therapy#	8
Current therapy	0

*: defined as: 0: normal; I: bilateral hilar lymphadenopathy (BHL); II: BHL with pulmonary infiltrates; III: pulmonary infiltrates without BHL. +: diagnosis is based on clinical data, although the biopsy was negative for sarcoid granuloma. In this setting patients whose chest radiograph showed stage 0 and III were excluded. #: patients who were treated with corticosteroid within 1 yr before the study were excluded.

Methods

All patients were prevented from being exposed to sunlight and received 500 mg of calcium and 1000 mg of phosphorus orally for 6 days before their blood and urine were examined. Urinary excretion of calcium was measured after the urine had been stored for 24 h. Hypercalciuria was diagnosed when the urinary excretion of calcium exceeded 0.3 $g \cdot day^{-1}$ in males, and 0.25 $g \cdot day^{-1}$ in females. sCa^{2+} was measured with an ion-sensitive electrode procedure, and its coefficients of variation (CV) were: interassay CV: 0.9% (low level), 0.4% (middle level) and 0.2% (high level); and intra-assay CV: 0.8% (low level), 1.1% (middle level) and 0.8% (high level). The adjusted concentration of serum calcium (adjCa) was calculated as (sCa $mg \cdot dL^{-1}$ + (4.0 - serum concentration of albumin $g \cdot dL^{-1}$))/ 4.01 $mmol \cdot L^{-1}$.

s1,25 $(OH)_2D_3$ was measured by radioreceptor assay (RRA) using $1,25(OH)_2D_3$ receptors derived from bovine mammary glands. The interassay CV were 8.78% (low level), 7.46% (middle level) and 11.6% (high level); and the intra-assay CV were 7.97% (low-level), 8.68% (middle level) and 16.7% (high level).

sPTH was measured by radioimmunoassay (RIA) using two antibodies specific to the fragment (from the 44th to 68th amino acids) of PTH. The interassay CV of this method were 10.06% (low level), 4.12% (middle level) and 5.87% (high level); and the intra-assay CV were 9.05% (low level), 6.21% (middle level) and 3.62% (high level).

sACE was measured with an optical density spectrometer at the wavelengths of 505 nm and 800 nm. The interassay CV were 4.15% (low level), 3.67% (middle level) and 2.80% (high level); and the intra-assay CV were 2.37% (low level), 1.79% (middle level) and 1.81% (high level).

Classification of chest radiographs was performed in accordance with the following classic criteria: stage 0: normal; stage I: BHL; stage II: BHL with pulmonary infiltrates; and stage III: pulmonary infiltrates without BHL. Every patient, even if asymptomatic, underwent ophthalmological examinations in order to detect uveitis and glaucoma. A dermatological biopsy was performed if the patient had a skin lesion suspected of being a sarcoid lesion. A thallium scan of the myocardium was performed when abnormal cardiac function was suspected on electrocardiography, or when an elevated cardiothoracic ratio was detected on chest radiography.

Informed consent about the restricted diet and all examinations to be carried out was obtained from each patient. This study was approved by the Ethical Committee of the Chest Disease Research Institute, Kyoto University.

Statistical analysis

Student's t-test and the Mann-Whitney U-test were used to compare two groups, and Pearson's method was selected for evaluating correlations. Using the receiver-operating characteristic (ROC) curve, discriminant analyses were performed to determine appropriate cut-off values [16].

Results

Incidence of hypercalcaemia and hypercalciuria

sCa and adjCa were above the normal range in three (9.8%) and two (5.6%) patients, respectively. In the same group sCa^{2+} were above the normal range in 10 patients (27.8%), of whom six (60.0%) were hypercalciuric. Twelve patients (33.3%) were hypercalciuric, of whom six (50.0%) showed increased sCa^{2+}. A history of nephrolithiasis had been detected in three patients. Values above the normal range for sCa, adjCa, sCa^{2+} or urine concentrations of (u)Ca, were detected in 16 patients (44.4%). Elevated levels of $s1,25(OH)_2D_3$ were shown in 5 patients (11.6%), four of whom were hypercalcaemic and/or hypercalciuric. One hypercalcaemic patient showed a decreased serum concentration of inorganic phosphorus (sPi) (see table 2).

Tentative cut-off value for sCa^{2+} to evaluate the presence of ETI

sCa^{2+} of patients with ETI and without ETI were 1.26± 0.10 mmol·L^{-1} and 1.21±0.02 mmol·L^{-1}, respectively (fig. 1). According to the ROC curve (fig. 2), a value of 1.23 mmol·L^{-1} of sCa^{2+} was determined as a cut-off value to evaluate the presence or the absence of ETI. In this report the sensitivity of this cut-off value was 50%, whereas the specificity was 100%. All 8 patients without ETI showed <1.23 mmol·L^{-1} of sCa^{2+}, whereas all patients who showed levels >1.23 mmol·L^{-1} of sCa^{2+} had ETI ($p<0.05$) (table 3).

Table 2. – Values related to calcium homeostasis in 36 patients with sarcoidosis*

	Mean±SD	Normal ranges
sCa mmol·L^{-1}	2.36±0.16	2.09–2.54
adjCa mmol·L^{-1}	2.19±0.19	2.09–2.54
sCa^{2+} mmol·L^{-1}	1.25±0.09	1.10–1.26
uCa g·day^{-1}		
Male	0.243±0.142	<0.3
Female	0.206±0.095	<0.25
sPi mg·dL^{-1}	3.4±0.4	2.5–4.5
$s1,25(OH)_2D_3$ pg·mL^{-1}	46.4±18.7	20–60
sPTH pg·mL^{-1}	281.7±99.0	260–560

sCa: serum concentration of calcium; adjCa: albumin-adjusted sCa; sCa^{2+}: serum concentration of ionized calcium; uCa: daily urinary excretion of calcium; sPi: serum concentration of inorganic phosphorus; $s1,25(OH)_2D_3$: serum concentration of 1,25-dihydroxyvitamin D; sPTH: serum concentration of parathyroid hormone. *: the serum angiotensin-converting enzyme activity (sACE) of these patients was 23.0±8.9 IU·L^{-1} (normal range 8.3–21.4).

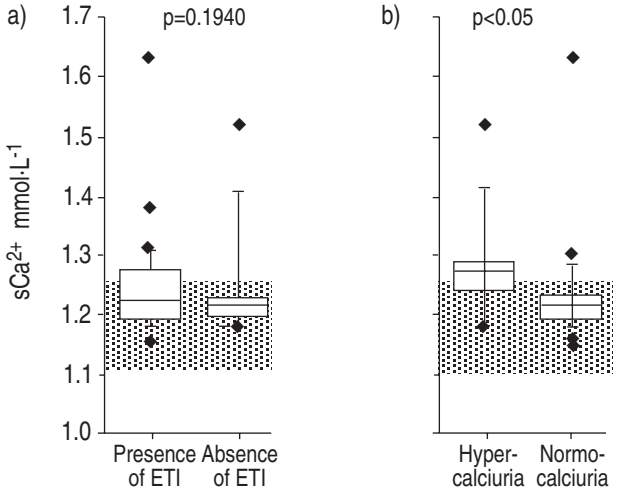

Fig. 1. – Box-whisker plots comparing serum concentration of ionized calcium (sCa^{2+}) between two groups of patients with sarcoidosis: a) presence *vs* absence of extrathoracic involvement (ETI); and b) hypercalciuria *vs* normocalciuria. Upper and lower bars indicate the 90th and 10th percentile, respectively, upper and lower margins of boxes indicate the 75th and 25th percentile, respectively, and the middle lines of the boxes indicate medians. Normal ranges are represented by the shaded zones. Significant difference between hypercalciuria and normocalciuria ($p<0.05$).

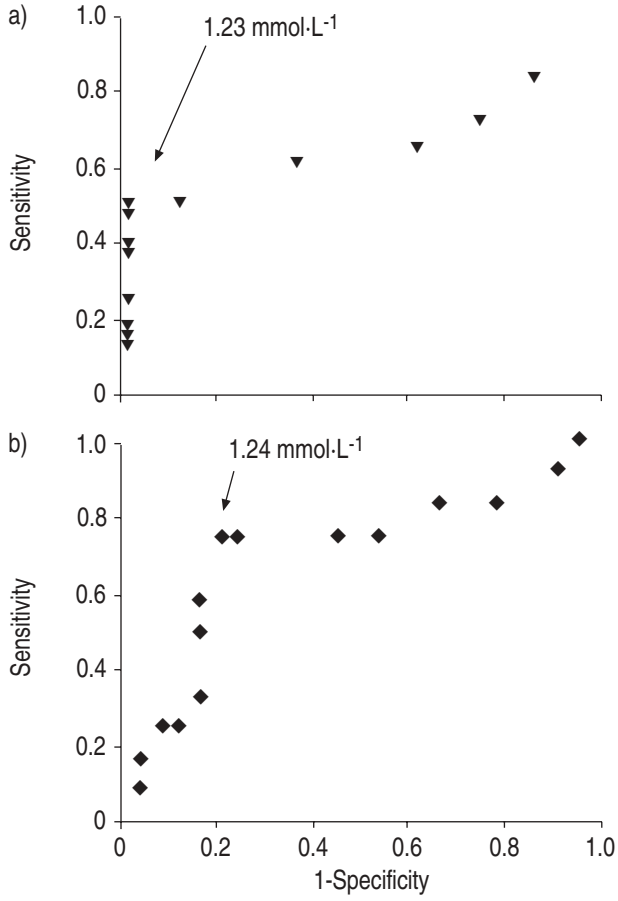

Fig. 2. – Receiver-operating characteristic (ROC) curves representing discriminant analyses with serum concentration of ionized calcium (sCa^{2+}): a) extrathoracic involvement; and b) hypercalciuria. The arrows inside the figures indicate cut-off values for sCa^{2+}: a) 1.23 mmol·L^{-1} and b) 1.24 mmol·L^{-1}.

Table 3. – Cut-off value of sCa^{2+} to evaluate the presence of ETI in patients with sarcoidosis

ETI	sCa^{2+} >1.23 mmol·L^{-1} n=14	sCa^{2+} ð1.23 mmol·L^{-1} n=22	
Present	14	14	
Absent	0	8	p<0.05

The cut-off value of 1.23 mmol·L^{-1} was determined with discriminant analysis using a receiver-operating characteristic curve. sCa^{2+}: serum concentration of ionized calcium; ETI: extrathoracic involvement.

Table 4. – Cut-off value of sCa^{2+} to evaluate hypercalciuria in patients with sarcoidosis

	sCa^{2+} >1.24 mmol·L^{-1} n=13	sCa^{2+} ð1.24 mmol·L^{-1} n=23	
Hypercalciuric	9	3	
Normocalciuric	4	20	p<0.01

The cut-off value of 1.24 mmol·L^{-1} was determined with discriminant analysis using a receiver-operating characteristic curve. sCa^{2+}: serum concentration of ionized calcium.

sACE and s1,25(OH)$_2$D$_3$ in patients with ETI and those without ETI

sACE in patients with ETI and without ETI were 24.1±9.3 IU·L^{-1} and 19.1±5.8 IU·L^{-1}, respectively (p=0.1594), and s1,25(OH)$_2$D$_3$ were 49.3±9.5 pg·mL^{-1} and 36.4±12.2 pg·mL^{-1}, respectively (p=0.0707).

sCa^{2+} as an index of hypercalciuria

Hypercalciuria was observed in six out of 10 patients who showed elevated sCa^{2+}. Six out of 12 hypercalciuric patients were normocalcaemic. The mean for sCa^{2+} was 1.28±0.09 mmol·L^{-1}, (normal range 1.10–1.26 mmol·L^{-1}) in hypercalciuric patients, which was significantly higher than the value of 1.23±0.09 mmol·L^{-1} (p<0.05) found in normocalciuric patients (fig. 1). With a discriminant analysis to evaluate hypercalciuria, using a ROC curve, 1.24 mmol·L^{-1} of sCa^{2+} was determined as a cut-off value (fig. 2). The sensitivity and specificity of this cut-off value were 75.0% and 83.3%, respectively, in this study. Nine out of 13 (69.2%) patients whose sCa^{2+} were above this cut-off value were hypercalciuric, while 20 out of 23 (87.0%) patients whose sCa^{2+} were less than this value were normocalciuric (p<0.01) (table 4).

Relations between sCa^{2+}, s1,25(OH)$_2$D$_3$ and sPTH

Ten patients showed sPTH below the normal range (230–560 pg·mL^{-1}): 171.1±31.4 pg·mL^{-1} (mean±SD), while 23 patients were within the normal range: 329.8±76.7 pg·mL^{-1} (sPTH was not measured in three patients). Among the 10 patients with low sPTH, four showed elevated sCa^{2+}, five were hypercalciuric and none showed elevated s1,25(OH)$_2$D$_3$. Four of these 10 patients showed no extranormal values of sCa^{2+}, uCa or s1,25(OH)$_2$D$_3$. Patients with low sPTH showed significantly higher values of sCa^{2+} than those with normal sPTH, 1.25±0.04 mmol·L^{-1} and 1.24±0.12 mmol·L^{-1}, respectively (p<0.05). No significant difference in s1,25(OH)$_2$D$_3$ was observed between the two groups.

Table 5. – Correlations among parameters of calcium metabolism in 36 patients with sarcoidosis

	r	p-value
sCa *vs* s1,25(OH)$_2$D$_3$	0.541	<0.001
adjCa *vs* s1,25(OH)$_2$D$_3$	0.552	<0.001
sCa^{2+} *vs* s1,25(OH)$_2$D$_3$	0.554	<0.001
uCa *vs* s1,25(OH)$_2$D$_3$	0.321	NS
sCa *vs* sACE	0.288	NS
adjCa *vs* sACE	0.423	<0.01
sCa^{2+} *vs* sACE	0.517	<0.001
uCa *vs* sACE	0.146	NS
sCa^{2+} *vs* sPTH	0.114	NS
sCa^{2+} *vs* sPi	-0.294	NS
sCa^{2+} *vs* uCa	0.300	NS
sPi *vs* sPTH	0.123	NS
sPi *vs* s1,25(OH)$_2$D$_3$	-0.011	NS
sPTH *vs* s1,25(OH)$_2$D$_3$	0.120	NS

NS: nonsignificant. For other abbreviations see legend to table 2.

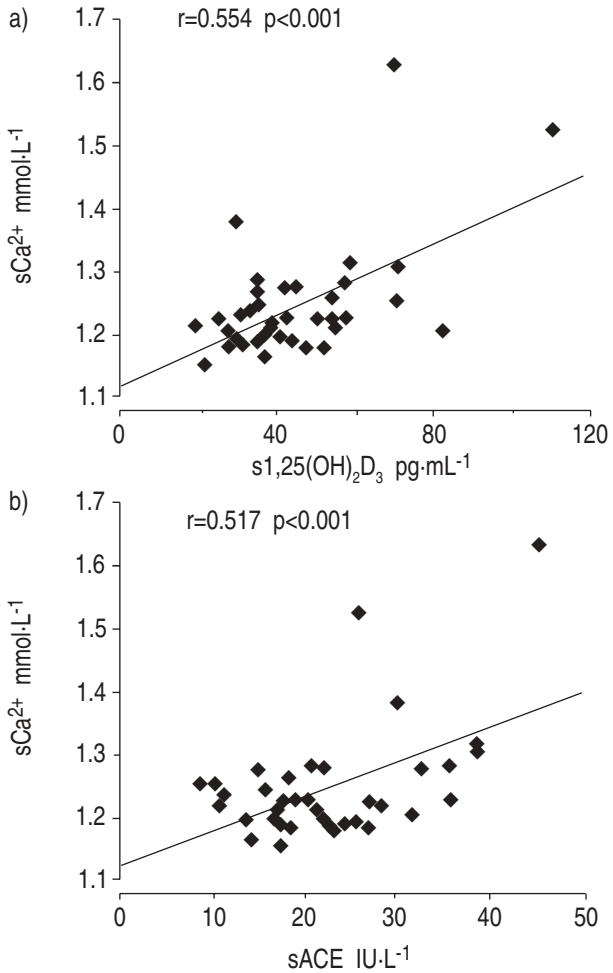

Fig. 3. – Correlation between a) serum concentration of 1,25-dihydroxyvitamin D (s1,25 $(OH)_2D_3$) and serum concentration of ionized calcium (sCa^{2+}) (r=0.554, p<0.001) and b) serum activity of angio-tensin-converting enzyme (sACE) and sCa^{2+} (r=0.517, p<0.001) in pati-ents with sarcoidosis. Normal ranges are: sCa^{2+}: 1.10–1.26 mmol·L^{-1}; s1,25(OH)$_2$D$_3$: 20–60 pg·mL^{-1}; sACE: 8.3–21.4 IU·mL^{-1}.

Correlations among indices

s1,25$(OH)_2D_3$ showed significant correlations with sCa, adjCa and sCa^{2+} (r=0.541, 0.552, 0.554, p<0.001, respectively) (table 5). sACE also showed significant correlations with adjCa and sCa^{2+} (r=0.423, p<0.01 and r=0.517, p<0.001, respectively). sPi showed no significant correlation with any index measured in this study. No significant correlation was detected between sACE and s1,25$(OH)_2D_3$ (fig. 3).

Discussion

In the current study imbalance of calcium homeostasis in patients with sarcoidosis was re-evaluated, using sCa^{2+} as an index. sCa and adjCa were elevated in only a few patients, whereas 27.8% of patients showed elevated sCa^{2+}. Using sCa^{2+} as an index, hypercalcaemia was observed rather commonly among Japanese patients with pulmonary sarcoidosis, even though it has been reported to be uncommon. An imbalance in calcium homeostasis was observed in 44.4% of the patients, which was almost the highest frequency ever reported [2, 9].

Hypercalciuria is an important clinical manifestation and a reflection of the disease activity of sarcoidosis. However thus far, its pathogenesis has not been precisely understood. The relation between serum concentration and daily urinary excretion of calcium did not seem to be simple and linear. In the current study, no significant correlation was observed between uCa and any other index, such as sCa, adjCa or sCa^{2+}. A discrepancy was observed between hypercalcaemia and hypercalciuria. Hypercalcaemic patients were not always hypercalciuric, and *vice versa*. That is, six (54.5%) out of 12 hypercalciuric patients were normocalcaemic, and five (50.0%) out of 10 hypercalcaemic patients (including those with elevated sCa^{2+}) were normocalciuric. Hypercalciuria with an elevated sCa suggests elevated calcium absorption from the intestine or resorption from the bone, whereas, hypercalciuria with a low sCa suggests calcium leakage from the kidneys [17]. In patients with sarcoidosis more than half of the hypercalciuric patients were normocalcaemic. There-fore, other factors such as alterations in the threshold of calcium excretion in kidneys may be taken into consideration, in addition to hypercalcaemia, to explain the pathogenesis of hypercalciuria in patients with sarcoidosis.

Whether or not sCa^{2+} could be useful as an index for disease activity for sarcoidosis was also investigated. sCa^{2+} showed a significant correlation with sACE, which has already been established as an index for disease activity of sarcoidosis [13, 18], although a direct pathophysiological relation between sCa^{2+} and sACE has not yet been described. Concomitant production of 1,25$(OH)_2D_3$ and ACE by activated macrophages and epithelioid cells in granulomas may play a crucial role in the correlation between sCa^{2+} and sACE, although no significant correlation was observed between sACE and s1,25$(OH)_2D_3$ in the current study.

Box-whisker plots of sCa^{2+} showed no significant difference between patients who had ETI and those who did not (fig. 1). In order to examine the relation to the presence of ETI, a discriminant analysis was performed, using a ROC curve (fig. 2). A low value of sCa^{2+} did not necessarily mean the absence of ETI, but a high value of sCa^{2+} (>1.23 mmol·L^{-1} in this study) strongly suggested the presence of ETI (p<0.05). Although the presence of ETI does not necessarily reflect either the disease activity itself or the total quantity of granulomas, it suggests systemic extension of sarcoid lesions.

Hypercalciuric patients showed higher sCa^{2+} than normocalciuric patients (p<0.05) (fig. 1). Another discriminant analysis was performed using the ROC curve, from which a cut-off value of 1.24 mmol·L^{-1} for sCa^{2+} was determined to evaluate hypercalciuria or normocalciuria (fig. 2). This discriminant analysis for evaluating hypercalciuria based on sCa^{2+} could be of clinical use, because uCa can be roughly evaluated without the 24 h storage of urine.

Two cut-off values for sCa^{2+} were tentatively determined in the current study, *i.e.* 1.23 mmol·L^{-1}, and 1.24 mmol·L^{-1}, for evaluating the presence of ETI and hypercalciuria, respectively. sCa and adjCa did not contribute to such discriminant analyses. These similar values seem to show a border range for evaluating the disease activity of sarcoidosis, although the number of cases studied was small. Further investigation should be performed with a sufficient number of cases in order to judge the feasibility of using sCa^{2+} to evaluate the disease activity of sarcoidosis.

s1,25$(OH)_2D_3$ showed higher values in patients with ETI, although this was not statistically significant. 1,25$(OH)_2D_3$ is reported not only to participate in calcium metabolism, but also to activate monocytes-macrophages and to promote their maturation [19–23], and, furthermore, to regulate and suppress T-cell activity [24–28]. It is possible that 1,25$(OH)_2D_3$ plays an important role in granuloma formation [3, 4, 29, 30]. In addition, recent studies revealed that the vitamin D binding protein itself is a precursor of the macrophage activating factor [31].

Although the migration and accumulation of activated T-cells are considered to precede granuloma formation, the granuloma consists of nothing more than maturing macrophages and epithelioid cells [32–35]. Since epithelioid cells might be one of the mature forms of mononuclear phagocytes, it would be worthwhile to investigate the precise pathophysiological role of vitamin D metabolism in sarcoidosis.

In normal subjects, the production of 1,25$(OH)_2D_3$ in the kidneys is strictly regulated by sCa^{2+}, sPTH and sPi [1]. A decrease in sPi or sCa^{2+} stimulates 25-hydroxyvitamin D-1α-hydroxylase in the kidneys, either directly or *via* mediation by PTH. An increase in s1,25$(OH)_2D_3$ suppresses the endocrine release of PTH from the parathyroid glands. Therefore, inverse correlations are expected between s1,25$(OH)_2D_3$ and each of such factors as sPi, sCa^{2+} and sPTH. As shown in table 5, however, any form of calcium concentration in the serum showed a significantly positive correlation with s1,25$(OH)_2D_3$, whereas sPi and sPTH did not show any significant correlation with s1,25$(OH)_2D_3$ in patients with sarcoidosis. However, as sCa^{2+} was higher in patients with low sPTH than in those with normal sPTH, an inverse correlation between sCa^{2+} and sPTH seemed to be probable. No clear evidence regarding the reciprocal regulation between sPTH and s1,25$(OH)_2D_3$ was seen in the current study.

The results support the former hypothesis that disease-related alterations to calcium metabolism in patients with sarcoidosis are induced by extrarenal 1,25$(OH)_2D_3$ which is produced within sarcoid granulomas, and that the production of 1,25$(OH)_2D_3$ is regulated not in a normal manner but in a substrate-dependent fashion.

In conclusion, imbalances of calcium homeostasis were clearly detected using sCa^{2+} as an index in Japanese patients with sarcoidosis. Elevated sCa^{2+}, suggesting the presence of ETI and hypercalciuria, was considered to reflect the disease activity of sarcoidosis.

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