Abstract

We previously reported a case in which steroid-induced psychosis was eliminated with risperidone treatment in a patient with polyarthritis nodosa (PN). In the present report, we longitudinally tracked the serum levels of brain-derived neurotrophic factor (BDNF). We found that corticosteroid lowered serum BDNF levels, and improvement of psychiatric symptoms was intact with the serum BDNF levels seen in the patients.

Introduction

There are several reports demonstrating the effectiveness of risperidone in treating steroid psychosis [1,2]. We have also previously demonstrated that risperidone did not change serum brain-derived neurotrophic factor (BDNF) levels in patients with schizophrenia [3]. BDNF is associated with psychiatric diseases such as depression or schizophrenia [1]. In the present case, risperidone rapidly diminished our patient's psychiatric symptoms without severe adverse effects. Corticosteroids suppress BDNF levels in the brain, which leads to atrophy of the hippocampus [4]. To the best of our knowledge, this is the first report showing longitudinal tracking of serum BDNF levels in a case of steroid psychosis in a patient with polyarthritis nodosa (PN).

Case presentation

Our patient, a 69-year-old woman, had had a diagnosis of PN for 4 years with no previous psychiatric history. Her major symptoms of PN were hypertension, pleuritis, vasculitis, a raised platelet count, and a high level of C-reactive protein. She did not have positive findings for vasculitis in the brain on MRI or magnetic resonance angiography (MRA). She had been treated with steroid pulse therapy (intravenous administration of methylprednisolone at 45 mg/day) followed by betamethasone at 4 mg/day. After 1 month at this dosage, she had experienced a mixed state that

included being more talkative than usual, feeling hyperactive, and excited, crying, feeling depressed, and having rapid mood swings, persecutory delusions, and auditory hallucinations. Her score on the Brief Psychiatric Rating Scale (BPRS) was 33 points. Risperidone was started at 1 mg/day and increased to 2 mg/day, and the dose of betamethasone was continued at the same dose (4 mg/day). Her psychiatric symptoms gradually improved, and she reached remission 3 weeks after the initiation of risperidone treatment. Since she demonstrated mild finger tremor, her dose of risperidone was decreased to 1 mg/day without worsening of her psychiatric symptoms. During her course of psychiatric symptoms, we longitudinally measured her serum BDNF levels, as shown in Figure 1.

Conclusions

Corticosteroid reduced serum BDNF levels and kept those levels lower, and risperidone did not cause the serum BDNF levels to recover. In addition, risperidone is effective for use in steroid psychosis patients with PN, and improvement of psychotic symptoms in the patient was independent of serum BDNF levels.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RY, KS, TT, NY and SH were crucially involved in the treatment process described for

our patient. WU-N assayed serum BDNF levels. KS, YT and JN critically revised the manuscript and gave their final approval for the version to be published.

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Figure legend

Figure 1. Changes in serum brain-derived neurotrophic factor (BDNF) levels and Brief Psychiatric Rating Scale (BPRS) scores.

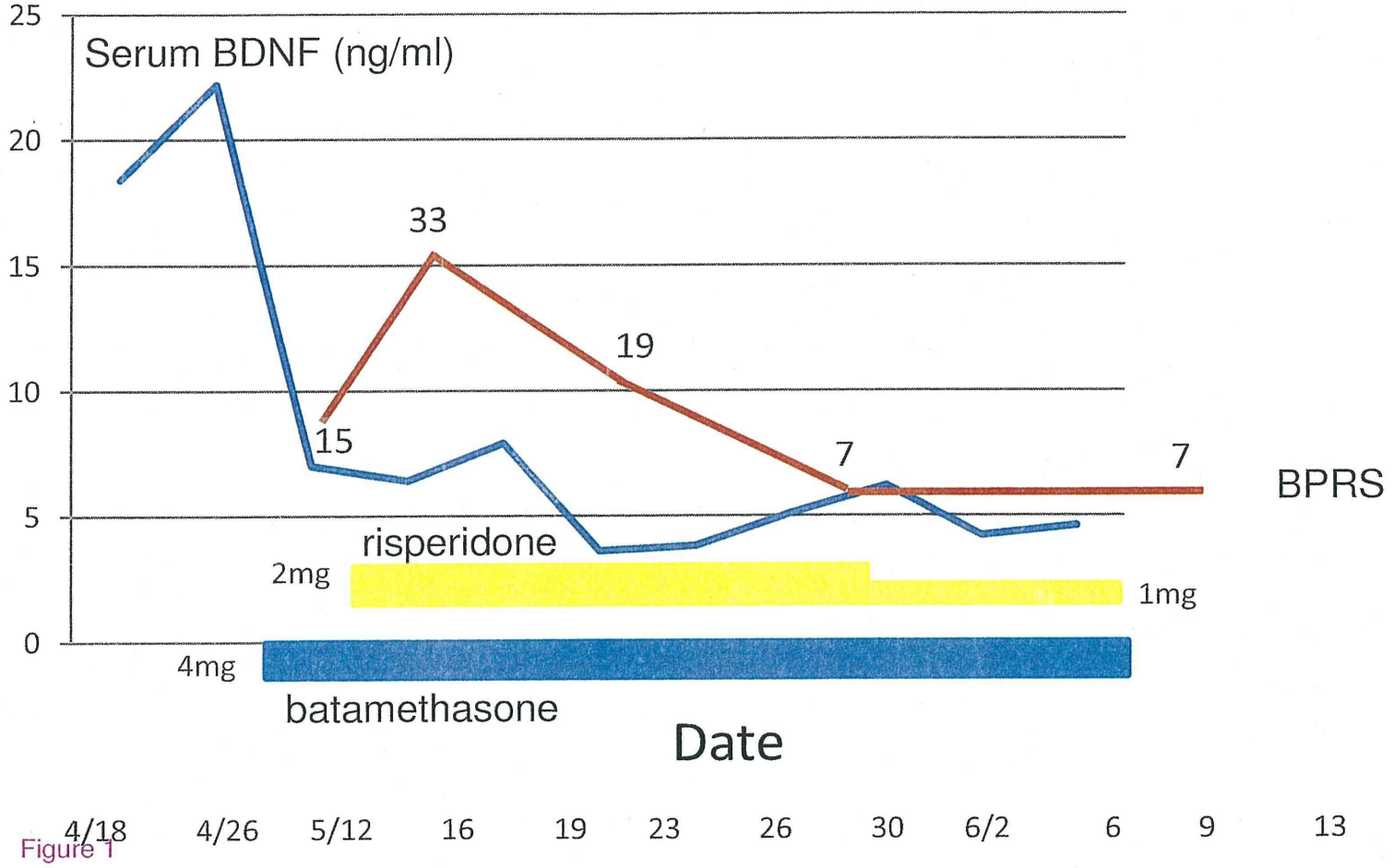
25
20
15
10
5
0
Serum BDNF (ng/ml)
33
19
15
7
7
BPRS
risperidone
2mg
1mg
4mg
batamethasone
Date
4/18
4/26
5/12
16
19
23
26
30
6/2
6
9
13

Figure 1

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ORIGINAL ARTICLE

Comparison of composite disease activity indices for rheumatoid arthritis

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Abstract To evaluate the composite disease activity indices for rheumatoid arthritis (RA), we compared disease activities and the changes therein calculated using the Disease Activity Score based on 28 joint counts using erythrocyte sedimentation rate (DAS28-ESR), DAS28-CRP (C-reactive protein), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) in a cohort of 1,412 patients with RA. The median (1st; 3rd quartile) scores were 4.20 (3.31; 5.14) for DAS28-ESR, 3.44 (2.59; 4.36) for DAS28-CRP, 13.6 (7.49; 21.1) for SDAI, and 12.0 (6.9; 18.9) for CDAI. Absolute scores and their changes were significantly correlated ($p < 0.0001$) in all combinations among these four disease activity indices; however, their correlations were lower in males than in females. Correlations between disease activity indices and the clinical and acute phase reactant variables were different according to disease activity index, sex and age. A comparison of the number of patients in each disease activity category according to the disease activity indices using kappa-statistics revealed an almost perfect agreement between SDAI and CDAI ($\kappa = 0.871$), a moderate agreement between DAS28-ESR and SDAI ($\kappa = 0.415$) or CDAI ($\kappa = 0.427$), but only fair agreement between DAS28-ESR and DAS28-CRP ($\kappa = 0.329$). For the selection of a disease activity index for an evaluation of RA patients, both the convenience and the characteristics of the respective disease activity index should be considered.

Keywords CDAI · DAS28 · Disease activity index · Rheumatoid arthritis · SDAI

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Introduction

The Disease Activity Score (DAS) is a major scoring system for evaluating disease activity in patients with rheumatoid arthritis (RA). The original DAS was developed by van der Heijde et al. in 1990 [1] and 1992 [2] and was based on the Ritchie articular index and the 44-swollen joint count [1, 2]. The original DAS was subsequently modified by a group of investigators from the Netherlands [3–5] to the DAS28, which is based on 28 joint counts [3] and is calculated using a formula which takes into account the number of tender joints (TJC) and swollen joints (SJC), the patient's global assessment of disease activity on a visual analog scale (VAS), and erythrocyte sedimentation rate (ESR). A more recent modification is the DAS28 using C-reactive protein (CRP) instead of ESR [6]. The use of

DAS and DAS28 in both clinical trials and daily clinical practice has been officially recommended by the European League Against Rheumatism (EULAR) [7]; however, these indices are difficult to use for an immediate determination in daily clinical practice due to their complexity and the need for a calculator.

Given these complexities, Smolen et al. proposed the Simplified Disease Activity Index (SDAI) in 2003 [8]. The SDAI is determined by a simple numerical summation of specific parameters, namely, the TJC and SJC of a 28-joint count, CRP, and the patient's and physician's global health assessment on a VAS (PGV and PhGV) [8], and it has been validated in several studies [9–12]. An additional index, the Clinical Disease Activity Index (CDAI), which is a modification of SDAI through the elimination of the CRP parameter, was introduced by Aletaha et al. in 2005 [13]. These two new indices (SDAI and CDAI) are convenient to use and thus easily applied in a clinical setting. However, studies comparing SDAI and CDAI with DAS28 have been limited [13].

In this study, we utilized the data of *NinJa* [14] (National Database of Rheumatic Disease by iR-net in Japan), which is a nationwide database of rheumatic diseases in Japan, and compared the four disease activity indices: DAS28 using ESR (DAS28-ESR), DAS28 using CRP (DAS28-CRP), SDAI, and CDAI. We also examined the differences in the influence of sex, age, and disease duration on the respective disease activity indices and their correlations, and on the correlations between each disease activity index and clinical and acute phase reactant variables.

Materials and methods

Data source and patients

The data source employed was a nationwide observational cohort database of rheumatic diseases in Japan named *NinJa* [14, 15]. The *NinJa* project was reviewed and approved by the research ethics committees of the National Hospital Organization, and all patients participating in the study provided informed consent.

In 2002 and 2003, a total of 2,799 and 4,026 patients with RA, respectively, were registered in *NinJa*. Of these, we analyzed the data of all patients who were registered in both 2002 and 2003 and for whom all of the data required for this study were obtainable. Data on patients registered in *NinJa* in 2003 were used for the cross-sectional study, and data on patients registered in *NinJa* in both 2002 and 2003 were used for the longitudinal study to examine the change in disease activity.

Of the 1,412 patients who satisfied the two inclusion criteria, 1,210 (85.7%) were female. The mean age of the patients registered in *NinJa* in 2003 was 60.1 years [standard deviation (SD) 10.6, range 18–89 years], and the mean disease duration was 14.7 years (SD 10.6, range 0–56 years) (Table 1). Most of the patients (n = 1,161, 82.2%) were taking disease-modifying anti-rheumatic drugs (DMARDs), 918 (65.0%) patients were taking corticosteroids, and 1,077 (76.3%) patients were using nonsteroidal anti-inflammatory drugs (NSAIDs). According to the data of *NinJa* 2003, no patients were treated with biologic agents.

Calculation and evaluation of respective disease activity indices

Calculations of DAS28-ESR, DAS28-CRP, SDAI, and CDAI were based on the following formulae:

Table 1 Demographic and disease characteristics of the patients

	NinJa 2002	*NinJa* 2003
Patients, *n*	1,412	
Age[a]	60.1 (10.6)	
Female, *n* (%)	1210 (85.7%)	
Disease duration[a]	14.7 (10.7)	
Disease activity score[b]		
DAS28-ESR	4.29 (3.43; 5.16)	4.20 (3.31; 5.14)
DAS28-CRP	3.59 (2.74; 4.47)	3.44 (2.59; 4.36)
SDAI	14.4 (8.41; 22.0)	13.6 (7.49; 21.1)
CDAI	12.9 (7.50; 19.5)	12.0 (6.91; 18.9)
Disease activity characteristics[b]		
Tender joint count (0–28)	2 (1; 5)	2 (1; 5)
Swollen joint count (0–28)	2 (2; 6)	1 (1; 4)
ESR (mm/h; normal < 20)	38 (20; 58)	40 (22; 60)
CRP (mg/dl; normal < 0.4)	0.83 (0.27; 2.30)	0.72 (0.22; 1.99)
mHAQ score (range 0–3)	0.50 (0.12; 1.00)	0.60 (0.12; 1.25)
Patient's pain VAS (10 cm)	3.4 (2.0; 5.3)	3.8 (2.0; 5.8)
Patient's global VAS (10 cm)	3.8 (2.1; 5.4)	4.1 (2.1; 5.7)
Physician's global VAS (10 cm)	3.1 (2.0; 4.9)	3.1 (1.8; 5.0)

SDAI Simplified Disease Activity Index, *CDAI* Clinical Disease Activity Index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *mHAQ* modified Health Assessment Questionnaire, *VAS* visual analog scale

[a] Age and disease duration are given in years as the mean, with the standard deviation (SD) given in parenthesis. Values are from the database of 2003

[b] Disease Activity Score and disease activity characteristics are given as the median, with the first and third quartile in parenthesis

$$\text{DAS28} - \text{ESR} = (0.56 \times \text{TJC}^{1/2}) + (0.28 \times \text{SJC}^{1/2}) + (0.7 \times \ln[\text{ESR}]) + (0.014 \times \text{PGV[in mm]})[7]$$

$$\text{DAS28} - \text{CRP} = (0.56 \times \text{TJC}^{1/2}) + (0.28 \times \text{SJC}^{1/2}) + (0.36 \times \ln[\text{CRP; in mg/l} + 1]) + (0.014 \times \text{PGV[in mm]}) + 0.96[7]$$

$$\text{SDAI} = \text{TJC} + \text{SJC} + \text{PGV(in cm)} + \text{PhGV(in cm)} + \text{CRP(in mg/dl)}[8]$$

$$\text{CDAI} = \text{TJC} + \text{SJC} + \text{PGV(in cm)} + \text{PhGV(in cm)}[13].$$

Patients were divided into those in remission (DAS28 < 2.6, SDAI < 3.3, CDAI < 2.8) and those with low (DAS28 < 3.2, SDAI < 11, CDAI < 10), moderate (3.2 ≤ DAS28 ≤ 5.1, 11 ≤ SDAI ≤ 26, 10 ≤ CDAI ≤ 22), and high disease activity (DAS28 > 5.1, SDAI > 26, CDAI > 22) according to the EULAR response criteria [4], SDAI [16], and CDAI disease activity categories [13], respectively. To evaluate the modified DAS28-CRP category for Japanese patients [17], cut-off points of remission (<2.3) and of low (<2.7), moderate (≥2.7, ≤4.1) and high disease activity (>4.1) were used, respectively.

Statistics

The Kolmogorov–Smirnov test was used to verify the normal distribution of data. Absolute scores and score changes were compared by calculating correlation coefficients (Spearman's rho) and by linear regression analysis to analyze the correlation among four composite disease activity indices [8, 12, 13]. The coefficient of determination (R^2) was used to compare the contribution of individual variables to composite scores [13]. The results for disease activity categorization were compared on a more individual basis by creating crosstabs and applying κ statistics. Cohen's κ measures the agreement between the evaluations of two raters when both are rating the same object [18]. A frequently cited rule of thumb [19] is that κ values >0.8 correspond to almost perfect agreement, those of 0.61–0.8 to substantial agreement, those of 0.41–0.6 to moderate agreement, and those of 0.2–0.4 to fair agreement. $\kappa = 0$ denotes chance agreement. Data processing and analyses were conducted with SPSS software (Windows release 11.0; SPSS, Chicago, IL, USA).

Results

Comparison of disease activity indices by cross-sectional analysis

SDAI and CDAI values were not normally distributed ($z = 3.133$ and 3.407, respectively; $p < 0.0001$) (Fig. 1). Therefore, the median values of the disease activity indices were compared. Using the data of patients registered in *NinJa* in 2003, the median (1st; 3rd quartile) scores were 4.20 (3.31; 5.14) for DAS28-ESR, 3.44 (2.59; 4.36) for DAS28-CRP, 13.6 (7.49; 21.1) for SDAI, and 12.0 (6.9; 18.9) for CDAI.

Using linear regression, we compared correlations of the four disease activity indices (DAS28-ESR, DAS28-CRP, SDAI, and CDAI). There was a strong correlations between DAS28-ESR and DAS28-CRP ($r = 0.942$, $p < 0.0001$) (Figs. 2a, 4a) and between SDAI and CDAI ($r = 0.985$, $p < 0.0001$) (Figs. 2f, 4a). Given that DAS28-CRP is derived from DAS28-ESR and that CDAI is derived from SDAI, the strong correlation noted above is not surprising and may be expected. Although calculated in different ways, SDAI and CDAI were also significantly correlated with DAS28-ESR ($r = 0.906$ and 0.895, respectively; $p < 0.0001$) and DAS28-CRP ($r = 0.955$ and 0.933, respectively; $p < 0.0001$) (Figs. 2b–e, 4a).

We checked the correlations among the indices by the Pearson's correlation coefficient after normalizing the distribution of the SDAI and CDAI scores by the Box–Cox transformation [20]. However, there was little difference between the data of the Pearson's correlation coefficient and that of the Spearman's rank correlation coefficient (data not shown).

Comparison of score changes of disease activity indices by longitudinal analysis

The mean score changes (SD) between the data of *NinJa* of 2002 and 2003 were −0.05 (0.03) for DAS28-ESR, −0.10 (0.03) for DAS28-CRP, −0.43 (0.26) for SDAI, and −0.20 (0.24) for CDAI. Figure 3 shows scatter plots of the score changes of disease activity indices. Similar to the cross-sectional analysis, score changes of all combinations among the four indices were highly correlated as follows: ΔDAS28-ESR versus ΔDAS28-CRP, $r = 0.927$; ΔDAS28-ESR versus ΔSDAI, $r = 0.858$; ΔDAS28-ESR versus ΔCDAI, $r = 0.847$; ΔDAS28-CRP versus ΔSDAI, $r = 0.914$; ΔDAS28-CRP versus ΔCDAI, $r = 0.880$; ΔSDAI versus ΔCDAI, $r = 0.969$ (all p values <0.0001) (Fig. 3).

Correlation of the disease activity indices with the respective clinical and acute phase reactant variables

To examine the differences in the correlation between a specific disease activity index and the respective clinical and acute phase reactant variables, namely, TJC and SJC of a 28-joint count [TJC (28) and SJC (28)], ESR, CRP, PGV, patient's pain VAS (PPV), PhGV, and modified health assessment questionnaire (mHAQ), we compared the coefficient of determination (R^2) between them.

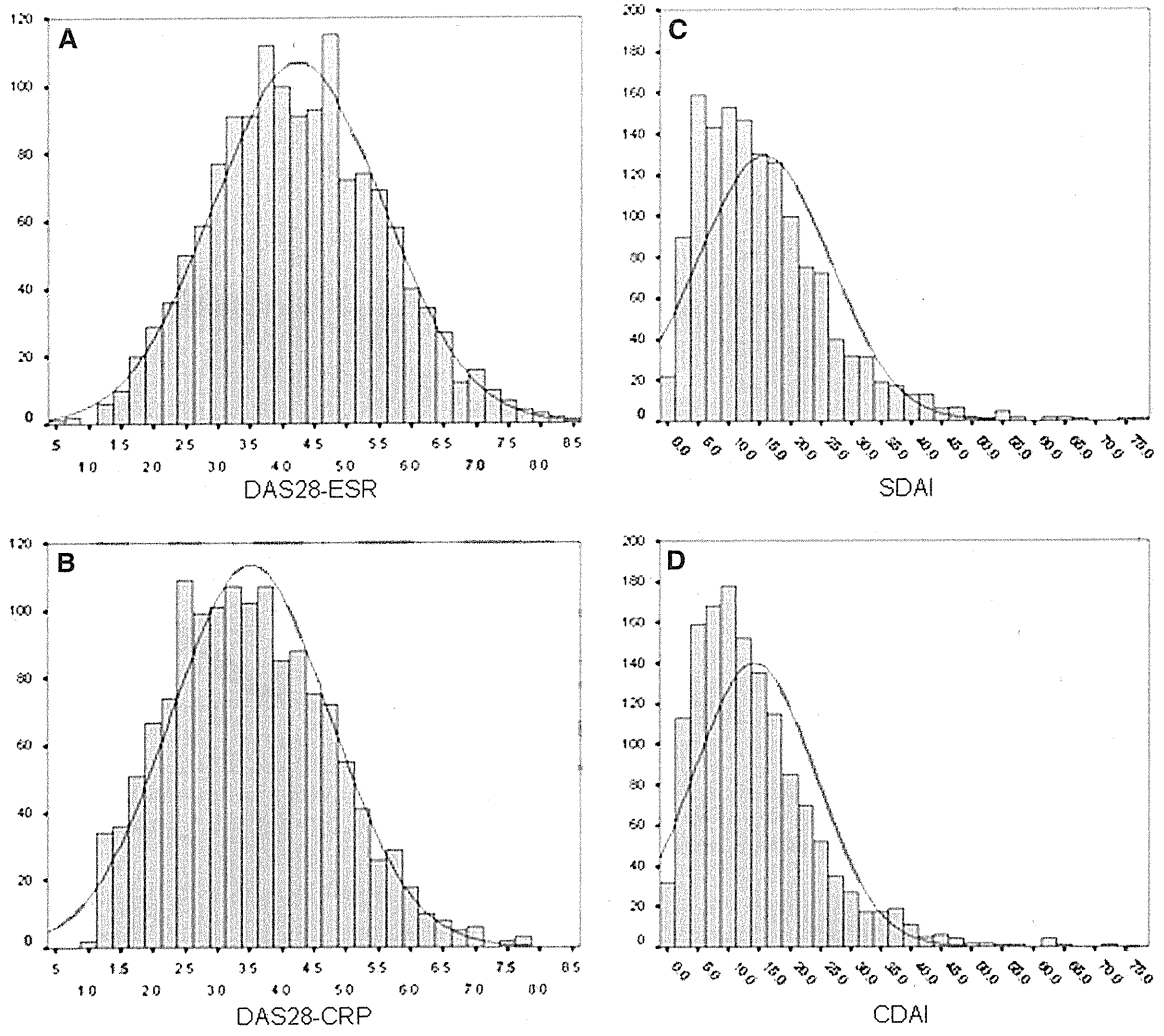

Fig. 1 Distribution of disease activity indices. Disease Activity Score based on 28 joint counts using erythrocyte sedimentation rate (*DAS28-ESR*; **a**), DAS28 using using C-reactive protein (*DAS28-CRP*; **b**), Simplified disease activity index (*SDAI*; **c**), and Clinical Disease Activity Index (*CDAI*; **d**) values in 1,412 patients with rheumatoid arthritis (RA) registered in the *NinJa* in 2003

The variable with the highest R^2 value was TJC (28) in DAS28-ESR, DAS28-CRP, and CDAI (64.0, 70.2, and 62.7%, respectively), whereas PhGV showed the highest R^2 value in SDAI (58.7%) (Fig. 5, see black bars in the figure). Other components of DAS28 [SJC (28), PGV, and ESR for DAS28-ESR, and SJC (28), PGV, and CRP for DAS28-CRP] had similar values of R^2 (around 40%) in each DAS28.

However, in SDAI and CDAI, their other components showed different values of R^2; that is, the value of R^2 of CRP was much smaller in SDAI (29.9%) and that of SJC (28) was smaller in SDAI (42.6%) and CDAI (44.6%) than other respective components (Fig. 5). The values of R^2 for acute phase reactants in SDAI (29.9% for CRP and 18.1% for ESR) and CDAI (18.6 and 12.4%, respectively) were lower than those in DAS28-ESR (31.8 and 40.7%, respectively) and DAS28-CRP (38.4 and 21.1%, respectively).

Effects of sex, age, and disease duration on the correlations of disease activity indices and their score changes

The correlations in males ($n = 202$) were slightly worse than those in females ($n = 1210$) in all combinations of disease activity indices (Fig. 4a) and their score changes (Fig. 4b). There was a tendency for the correlation coefficient in all combinations of disease activity indices to become lower with increasing age (Fig. 4a), but their score changes did not show this tendency (Fig. 4b). There were no obvious tendencies related to disease duration (data not shown).

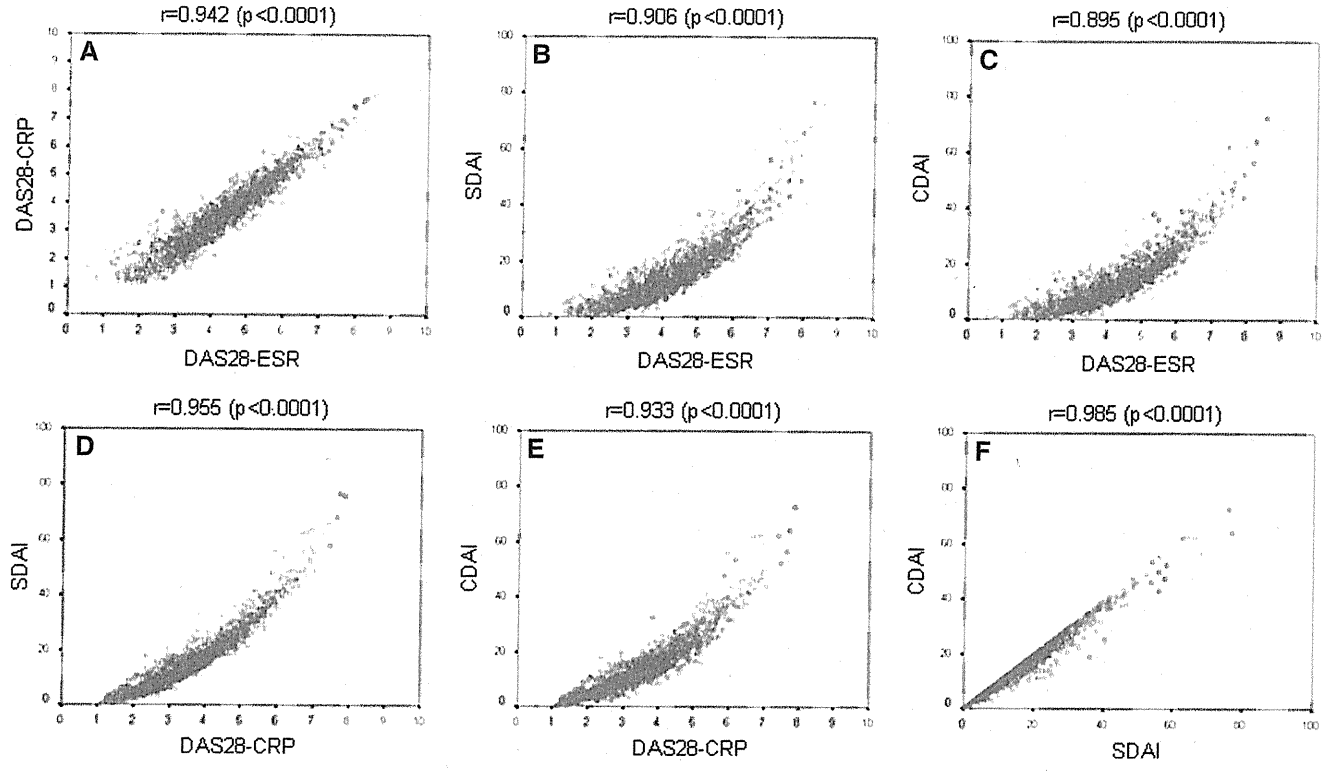

Fig. 2 Scatter plots of the continuous disease activity indices. All linear regression analyses indicate a highly significant degree of correlation between the continuous disease activity indices. **a** DAS28-ESR versus DAS28-CRP, **b** DAS28-ESR versus SDAI, **c** DAS28-ESR versus CDAI, **d** DAS28-CRP versus SDAI, **e** DAS28-CRP versus CDAI, **f** SDAI versus CDAI

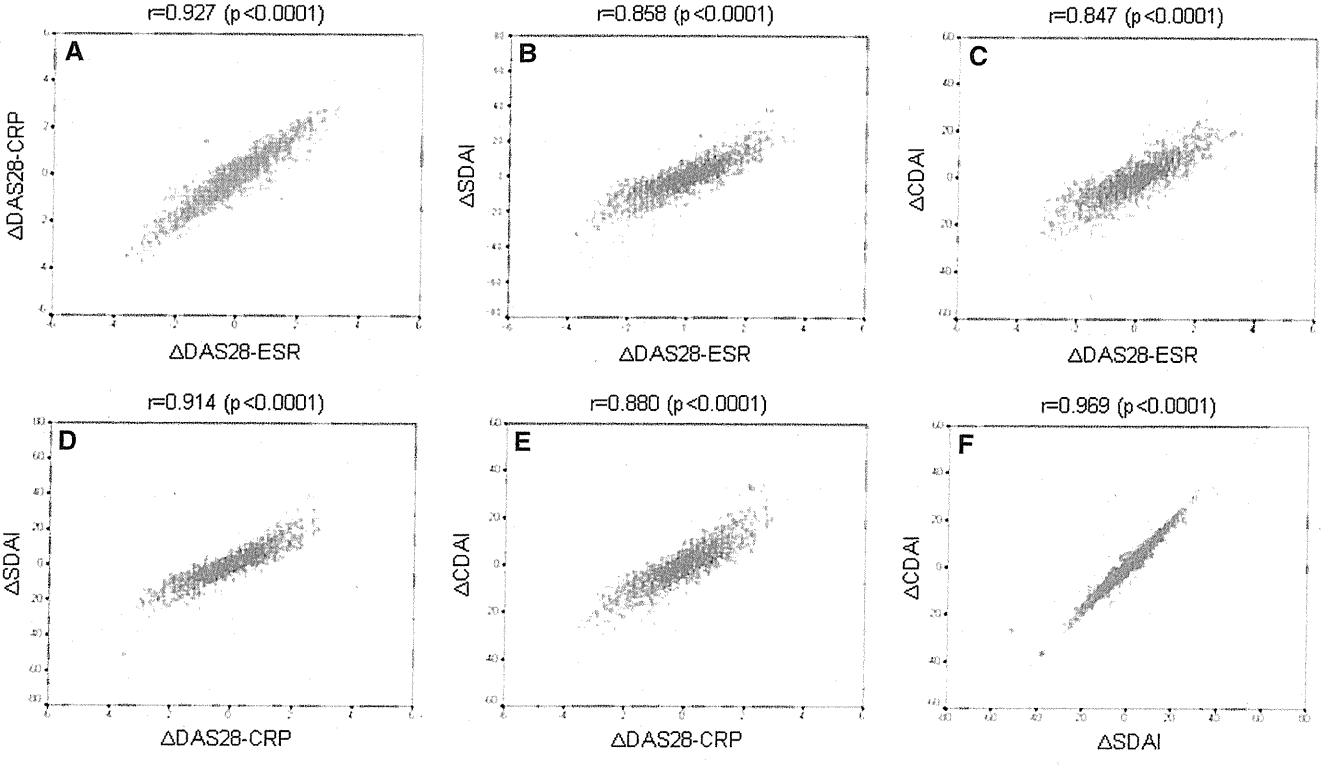

Fig. 3 Scatter plots of the change in the continuous disease activity indices. All linear regression analyses indicate a highly significant degree of correlation between the changes in the continuous disease activity indices. **a** DAS28-ESR versus DAS28-CRP, **b** DAS28-ESR versus SDAI, **c** DAS28-ESR versus CDAI, **d** DAS28-CRP versus SDAI, **e** DAS28-CRP versus CDAI, **f** SDAI versus CDAI

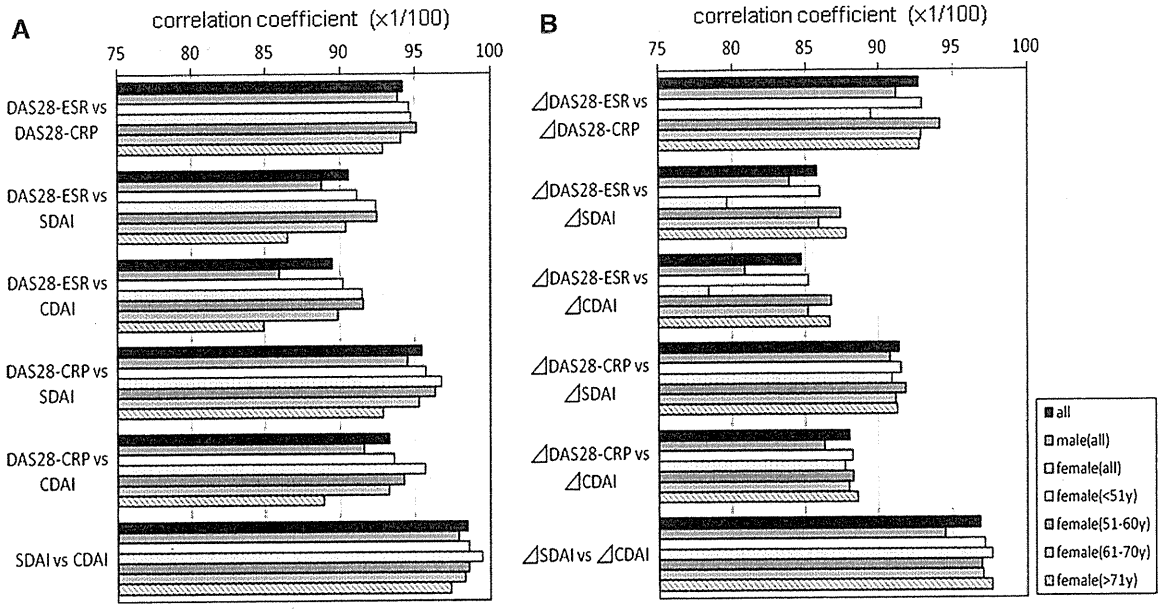

Fig. 4 Correlation of disease activity score and their changes between disease activity indices. Absolute scores and score changes stratified by sex and age are compared by calculating correlation coefficients (Spearman's rho). The correlation of disease activity score (**a**) and their changes (**b**) are shown. Score changes (⊿) are the differences between the data compiled in the 2002 and 2003 *NinJa*

Effects of sex, age, and disease duration on the correlations between the disease activity index and the respective clinical and acute phase reactant variables

To examine the effects of sex, age, and disease duration on the correlations between the disease activity index and the respective clinical and acute phase reactant variables, we compared the coefficient of determination (R^2) between them.

With respect to the correlations between the disease activity index and the respective clinical and acute phase reactant variables, there were similar trends in males and females as in the total scores described above. However, values of R^2 of acute phase reactants in males were higher than those in females, and other variables in males were lower than those in females for all indices (Fig. 5).

For the comparison between age groups in females, the variable with the highest R^2 was the same in each age group (except for that over 71 years in SDAI) as that for the total female patient cohort [TJC (28) in DAS28-ESR, DAS28-CRP, and CDAI, and PhGV in SDAI]. However, the rank order of R^2 (i.e., 2nd, 3rd, 4th, etc.) for the other variables differed among the different age groups in all indices (Fig. 5). There were no obvious tendencies related to disease duration (data not shown).

Disease activity categorization

The number (rate) of patients in each category of disease activity according to the disease activity indices is summarized in Table 2. The rate of remission and low disease activity was much higher and that of high disease activity was much lower according to the DAS28-CRP than the DAS28-ESR. With the SDAI and CDAI, the rate of remission and high disease activity was lower; however, that of low disease activity was apparently higher than in DAS28-ESR. Using the modified DAS28-CRP category for Japanese patients [17], the rate of remission and low disease activity decreased, but that of high disease activity increased by threefold times relative to that indicated by the original DAS28-CRP.

We then analyzed the distribution of the categorized patients in other disease activity index categories and investigated their agreement by κ statistics (Fig. 6). An almost perfect agreement was found in the relationship between SDAI and CDAI ($\kappa = 0.871$), and a moderate agreement was found between DAS28-ESR and SDAI ($\kappa = 0.415$) or CDAI ($\kappa = 0.427$). For the relationship between DAS28-ESR and DAS28-CRP, κ value was only 0.329 (fair agreement); however, their κ value increased to 0.616 (substantial agreement) using modified DAS28-CRP category for Japanese patients (Table 2; Fig. 6).

Discussion

In this study, we showed that the four disease activity indices evaluated (DAS28-ESR, DAS28-CRP, SDAI, and CDAI) were significantly correlated with each other in both absolute scores and score changes. Aletaha et al. [13] reported that

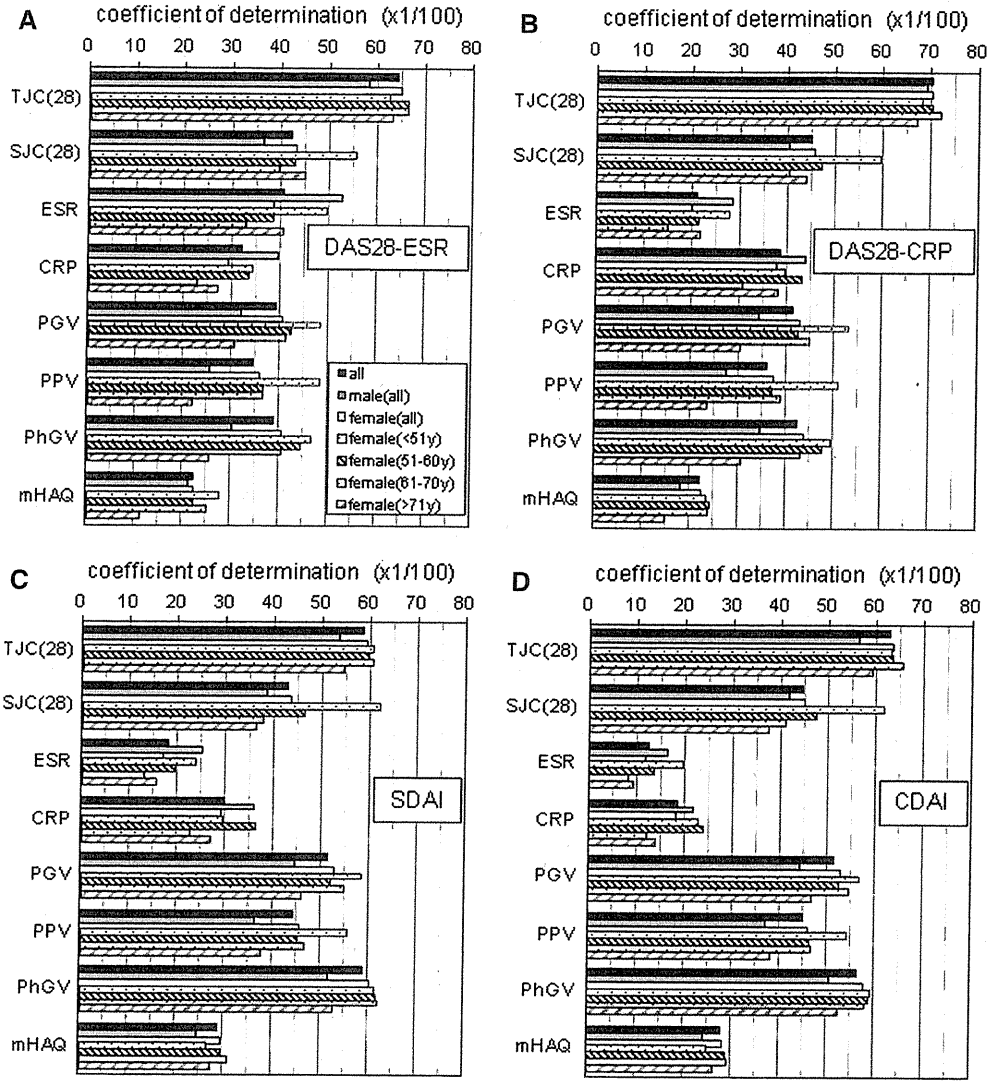

Fig. 5 Contribution of individual variables to composite scores. Coefficient of determination (R^2) of individual variables to DAS28-ESR (**a**), DAS28-CRP (**b**), SDAI (**c**), and CDAI (**d**) stratified by sex and age. *TJC(28)/SJC(28)* Tender/swollen joint count (28 joints) *PGV/PPV/PhGV* patient's global/patient's pain/physician's global assessment on visual analogue scale, *mHAQ* modified Health Assessment Questionnaire

Table 2 Category of patients according to each disease activity index

Category	DAS28-ESR	DAS28-CRP	SDAI	CDAI	DAS28-CRP(J)[a]
Remission	147 (10.4)	353 (25.0)	93 (6.6)	93 (6.6)	240 (17.0)
Low[#]	314 (22.2)	605 (42.8)	551 (39.0)	557 (39.4)	403 (28.5)
Moderate	734 (52.0)	651 (46.1)	656 (46.5)	605 (42.8)	563 (39.9)
High	364 (25.6)	156 (11.0)	205 (14.5)	250 (17.7)	446 (31.6)

Data are presented as the number with the percentage in parenthesis

Low[#] disease activity category includes patients in the remission category. Each cut-off point of the other disease categories is as follows; remission: 2.6 in DAS28-ESR and DAS28-CRP, 3.3 in SDAI, and 2.8 in CDAI; low: 3.2 in DAS28-ESR and DAS28-CRP, 11 in SDAI, and 10 in CDAI; high: 5.1 in DAS28-ESR and DAS28-CRP, 26 in SDAI, and 22 in CDAI

[a] DAS28-CRP(J): the modified DAS28-CRP category for Japanese patients [18]. Each categories were as follows; remission (<2.3), low (<2.7), moderate (≥2.7, ≤4.1) and high disease activity (>4.1)

absolute scores of DAS28-ESR, SDAI, and CDAI were significantly correlated, with very similar values of correlation coefficients as our results. However, to the best of our knowledge, this is the first report describing correlations among score changes in these four disease activity indices and the influences of sex, age, and disease duration on the respective index and on the correlations between the indices and clinical and acute phase reactant variables.

In all indices, TJC (28) showed high values of R^2 among the variables examined here. This may be expected because

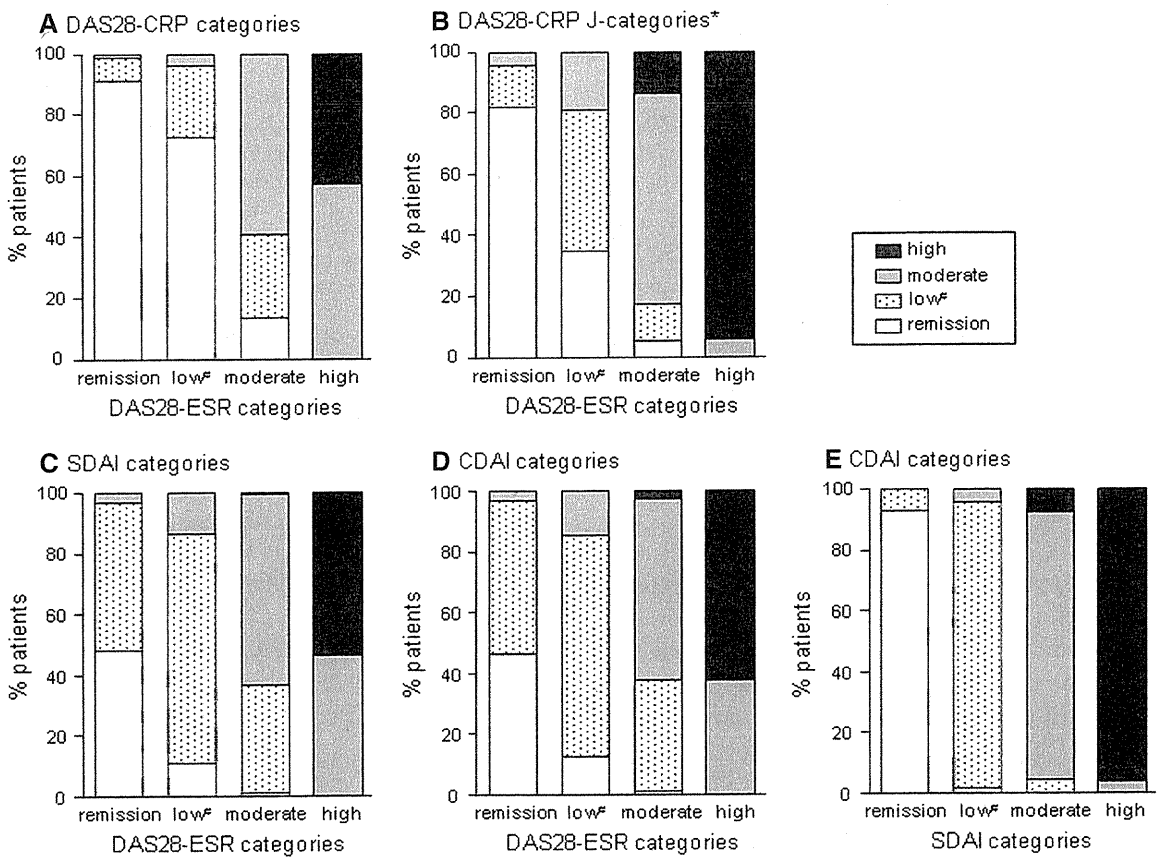

Fig. 6 Distribution of categorized patients. **a** DAS28-CRP versus DAS28-ESR, **b** DAS28-CRP J versus DAS28-ESR, **c** SDAI versus DAS28-ESR, **d** CDAI versus DAS28-ESR, **e** CDAI versus SDAI. Note that low# disease activity category in this figure does not include patients in the remission category. **DAS28-CRP J* DAS28-CRP modified for Japanese patients; the categories were: remission (<2.3), low (<2.7), moderate (≥2.7, ≤4.1), and high (>4.1) disease activity [17]

in both DAS28 calculations, the weight of TJC (28) is twofold that of SJC (28) in the respective formulae. However, for SDAI and CDAI, values of R^2 in TJC (28) are higher than those in SJC (28) in all categories, even though their weights are equal in their respective formulae. These results indicate that TJC (28) is a common major factor in all indices, with the highest R^2, but for the other variables, the rank order of values of R^2 (i.e., 2nd, 3rd, 4th, etc) differ among the four indices. VAS in both SDAI and CDAI showed higher values of R^2 than that in DAS28, and their R^2 values were apparently higher than those of acute phase reactants in each index. This may be because (1) PGV and PhGV are included in both these formulae, (2) there is a different distribution of the values between VAS (median 3.1–4.8 cm) and CRP (median 0.72 mg/dl) which are simply added in the formula of SDAI, and (3) acute phase reactants are not included in the formula of CDAI.

Sex and age had some influence on the values of R^2 between the respective indices and clinical and acute phase reactant variables. All of the variables except acute phase reactants (ESR and CRP) showed higher R^2 values in females than in males. ESR is well known to be affected by sex [21, 22], and its normal range is usually set differently for females and males, but it is not common that sexual differences exist among the other variables, including CRP. Further studies are needed to examine the influence of sex on these variables. For the comparison between age groups in females, the rank order of R^2 differed among the different age groups, whereas the variable with the highest R^2 was the same as that in the total female patients in all indices. However, our data indicated that sex and age had only a slight effect on the correlation coefficient among these indices and their changes (Figs. 4, 5). These results suggest that we do not have to pay much attention to sex and age of the patients when choosing a composite disease activity index.

There was a difference among the numbers of patients categorized by the EULAR response criteria, SDAI criteria, and CDAI criteria (Table 2, Fig. 6). In particular, the rate of patients in remission/low disease activity was clearly different among the respective criteria. Although there was a moderate agreement in categorization between DAS28-ESR and SDAI or CDAI, remission according to the SDAI and CDAI was achieved in fewer patients than remission according to the DAS28; this result is in agreement with

previous findings [16, 23]. Aletaha [16] reported that the average level of residual disease activity in DAS28 remission was different from the levels in patients in SDAI or CDAI remission and that DAS28 allows patients to be classified as "in remission" despite the presence of residual swollen joints (up to 13/28 joints) or high PGV (up to 67/100 mm). In contrast, the rate of low disease activity was much higher in SDAI and CDAI than in DAS28-ESR. In DAS28-CRP, the overall underestimation of disease activity was observed as previously reported [17, 24]. Furthermore, there was a fair agreement ($\kappa = 0.329$) in terms of categorization between DAS28-ESR and DAS28-CRP. Inoue et al. [17] suggested a modified DAS28-CRP category, which could increase the κ value to 0.616 (substantial agreement) in our dataset. The newest EULAR recommendation for the management of RA proposes that the therapeutic target should be remission or low disease activity [25]. Therefore, these inconsistent categorizations are critical as well as being confusing to the physician who has to choose which index to use for evaluating patients. Further studies on the validation of categorization according to the composite disease indices are necessary.

Therefore, which indices should we select for evaluating and monitoring patients with RA? As mentioned above, the aim of the newest EULAR recommendation is the tight control of the disease activity targeting "remission" or "low disease activity" using any of the composite disease activity indices. For this purpose, "simplicity" and "convenience" are more expected for the composite disease activity index in daily clinical practice. Given their simplicity of calculation, the SDAI and CDAI are suitable because they are applicable without any electric device. Moreover, the CDAI is very convenient for use in a disease activity evaluation without an acute phase reactant. The asymmetrical distribution of the SDAI and CDAI scores may affect the evaluation of disease activity; however, our data show that not only the absolute scores but also their score changes are highly significantly correlated between DAS28 and SDAI or CDAI. In addition, the remission criteria are more stringent in SDAI and CDAI than in DAS28. It is true that SDAI and CDAI have some limitations relative to the DAS28 in terms of an evaluation of disease activity, but they may have some advantages for monitoring RA patients in daily clinical practice.

In conclusion, in our Japanese patient cohort, the DAS28-ESR, DAS28-CRP, SDAI, and CDAI were well correlated with each other as a total score. However, the contribution of the respective variables was different for disease activity index, sex, age, and disease duration. For the selection of a disease activity index for the evaluation of RA patients, both the convenience of use and also the characteristics of the respective disease activity indices should be considered.

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Conflict of interest None.

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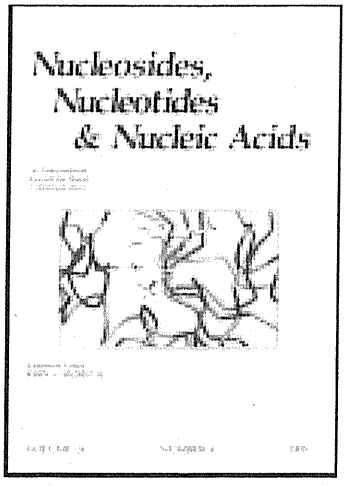

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Japanese Guideline for the Management of Hyperuricemia and Gout: Second Edition

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JAPANESE GUIDELINE FOR THE MANAGEMENT OF HYPERURICEMIA AND GOUT: SECOND EDITION

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□ *Gout is a urate deposition disease caused by persistent hyperuricemia. Because gout patients present with a variety of clinical symptoms, it is necessary to have a guideline for the standard management and care of gout and hyperuricemia. The Japanese Society of Gout and Nucleic Acid Metabolism, a scientific society committed to study nucleic acid metabolism and related diseases, established the first edition of the "Guideline for the Management of Hyperuricemia and Gout" in 2002, and published the revised version in January 2010. This second edition is not only evidence based on a search of systemic literature, but also includes consensus levels by a Delphi exercise to determine the strength of the recommendations. A draft version of this guideline was reviewed by internal and external reviewers as well as a patient. In this guideline, key messages from each chapter are listed as statements together with the evidence level, consensus level, and strength of the recommendation. In this proceeding, several selected chapters on the clinical management of gout and hyperuricemia are described. We hope this guideline is appropriately used for the standard management and care of patients with hyperuricemia and gout in daily practice.*

Keywords Guideline; gouty arthritis; hyperuricemia

INTRODUCTION

Gout is a urate deposition disease caused by persistent hyperuricemia. Because gout patients present with a variety of clinical symptoms, including acute arthritis, urinary stones, chronic kidney disease, and metabolic syndromes, they are often treated by physicians from a variety of subspecialties; thus, it is necessary to have a guideline for the management of gout and hyperuricemia. For this purpose, the Japanese Society of Gout and Nucleic Acid Metabolism, a scientific society established to study nucleic acid metabolism and related diseases, published the first edition of the "Guideline for the Management of Hyperuricemia and Gout" in 2002. Since its publication, additional data concerning the management of hyperuricemia

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and gout have accumulated, and the circumstances surrounding the clinical guidelines have also changed. Therefore, the Japanese Society of Gout and Nucleic Acid Metabolism established a committee to revise the guideline (Chairman: Hisashi Yamanaka, M.D.) in 2006. The committee actively collected data related to hyperuricemia and gout and discussed the significance of this information in daily practice. Ultimately, the second edition was published in January 2010.

MATERIALS AND METHODS

The guideline revising committee collected clinical questions for the management of gout and hyperuricemia, and based on 41 clinical questions, a systematic literature search was conducted. From the results of this search, 492 articles were selected and reviewed by committee members, and recommendations for the management of gout and hyperuricemia were proposed as statements with evidence levels. Next, a Delphi exercise[1] was conducted to determine the consensus level of each statement, and the strength of the recommendations in each statement was determined based on both the evidence level and the consensus level.

Evidence Levels

- Evidence level 1a: Evidence obtained by a meta-analysis of randomized comparative trials (RCTs) and results obtained by multiple RCTs are almost consistent.
- Evidence level 1b: Evidence obtained by at least one RCT.
- Evidence level 2a: Evidence obtained by well-designed, comparative studies (nonrandomized), including prospective cohort studies.
- Evidence level 2b: Evidence obtained by well-designed, semi-empirical studies, including retrospective studies.
- Evidence level 3: Evidence obtained by well-designed, nonempirical, descriptive studies, including case control studies.
- Evidence level 4: Evidence obtained from case reports, noncontrolled studies, low-quality cohort studies, and cross-sectional studies.
- Evidence level 5: Evidence obtained by expert's reports/opinions/experience, etc.

Consensus Levels

Consensus levels were assessed using a seven-rank rating, wherein rank 1 indicated a full consensus; rank 4, neutral; and rank 7, no consensus.

Recommendation Levels

On the epidemiology/diagnosis of gout/hyperuricemia (Chapters 1 and 2):

- Recommendation level A: Based on strong evidence for certainty.
- Recommendation level B: Based on evidence for certainty.
- Recommendation level C: Based on no evidence for certainty.

On the therapy for gout/hyperuricemia (Chapters 3 and 4):

- Recommendation level A: Therapy is strongly recommended.
- Recommendation level B: Therapy is recommended.
- Recommendation level C: Therapy may be considered for certain cases.

The consistency of the contents of this guideline with those of other guidelines was reviewed and confirmed by liaison members of the committee. A draft version of this guideline was reviewed by trustee members of the Japanese Society of Gout and Nucleic Acid Metabolism, and subsequently, public comments were requested by external reviewers. Finally, the patient perspective was included based on the review of this guideline by a gout patient who works in the field of medical journalism. After these careful reviews, the Japanese Guideline for the Management of Hyperuricemia and Gout, second edition, was published in January 2010. The European League Against Rheumatism (EULAR) Standing Committee has published a recommendation for the management of gout[2,3]; however, a major difference between this guideline and the EULAR recommendation is that this guideline covers the management not only of gout but also of hyperuricemia.

RESULTS AND DISCUSSION

In this manuscript, the key messages from each chapter are listed together with the evidence level, consensus level, and strength of the recommendation. In this proceeding, several selected chapters on the clinical management of gout and hyperuricemia are presented.

Definition of Hyperuricemia

Statements:

1. Hyperuricemia is a major pathogenic factor for urate deposition diseases (gouty arthritis, renal disorder, etc.). It is defined as a disease condition in which patients have a serum urate level exceeding 7.0 mg/dL, regardless of sex and age—Evidence level 2a and Recommendation level B.

2. In women, the risks of lifestyle-related diseases increase with increases in the serum urate level, even when it is not more than 7.0 mg/dL. Examination for possible underlying diseases and lifestyle guidance should be given; however, drug therapy with urate-lowering drugs is not indicated—Evidence level 2a and Recommendation level B.

In the "Guideline for Therapy of Hyperuricemia/Gout (Version 2)", the significance of the serum urate level is evaluated from two viewpoints:

(1) Hyperuricemia as the cause of urate deposition diseases, such as gouty arthritis and renal impairment.
(2) Serum urate level as a clinically useful index (marker) of the pathology of various lifestyle-related diseases.

Hyperuricemia is a causative factor of urate deposition diseases, and the efficacy of therapeutic intervention has been confirmed. Hyperuricemia is a clear risk factor for gouty arthritis, the recurrence of which is suppressed by therapeutic interventions. Metabolic syndrome has attracted attention, and the results of an analysis focusing on the risks of cardiovascular diseases have demonstrated that a high serum urate level is also predictive of the onset of lifestyle-related diseases. However, the significance of urate in such pathologic conditions is unclear. Furthermore, reports indicating the improvement of these pathologic risks by therapeutic interventions are unavailable to date.

Taking these points into consideration, we suggest that attention should be given to the fact that the risks of lifestyle-related diseases increase with increases in serum urate level in both males and females, even if it is less than 7.0 mg/dL.[4] Examinations of potential diseases and lifestyle guidance are recommended at a lower serum urate level in females than in males. However, the risks increase linearly; thus, no clear threshold of serum urate level against the risk for diseases, including cardiovascular diseases, was determined. Also, urate-lowering drugs are currently not recommended for such cases (Figure 1).

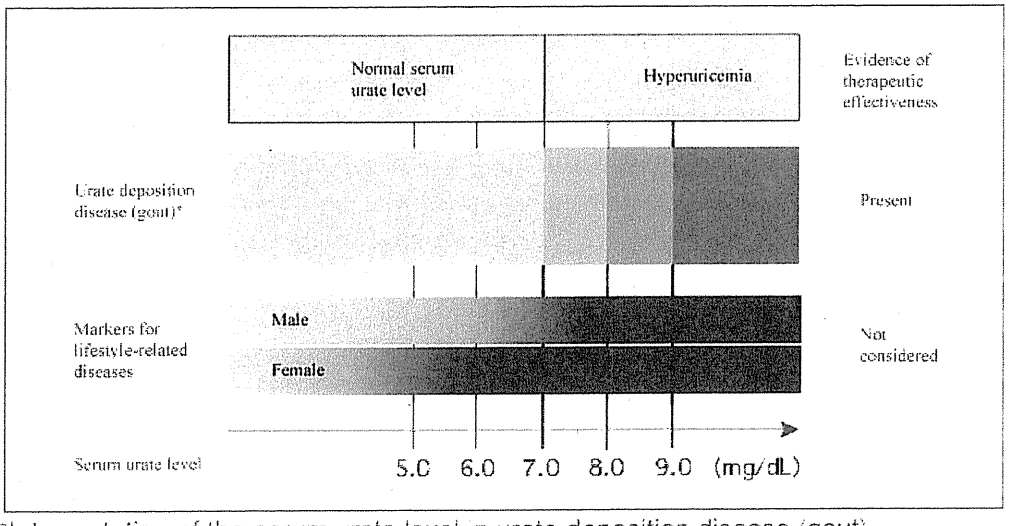
Therapy of Gouty Arthritis/Gouty Tophus

Statements:

1) One tablet of colchicine (0.5 mg) is used in the aura phase of a gouty attack to stop further development of arthritis. In the case of frequent occurrences of gouty attacks, daily medication with one tablet of colchicine, "colchicine cover," is effective—Evidence level 3, Consensus level 1, and Recommendation level B.

2) Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in the acute phase of a gouty attack. NSAIDs are administered at a relatively high dose for a limited period to alleviate inflammation (NSAID pulse therapy). Accordingly, the occurrence of adverse drug reactions should be noted—Evidence level 3, Consensus level 1, and Advisability level B.
3) Oral corticosteroids are administered when NSAIDs cannot be administered, when NSAID administration is ineffective, or when polyarthritis occurs—Evidence level 1a, Consensus level 1, and Recommendation level A.
4) Since a gouty attack is exacerbated when the serum urate level is changed at the time of attack, in principle, medication with uric-acid-lowering drugs should not be initiated—Evidence level 3, Consensus level 1, and Advisability level B.
5) Surgical resection is considered necessary in the treatment of some cases of gouty tophus, but drug therapy is also necessary in such cases—Evidence level 3, Consensus level 1, and Recommendation level B.

A gouty attack is acute arthritis caused by urate crystals. Alleviating patients' pain and improvement of their quality of life (QOL) by appropriate therapy are the objectives of treatment.[5–7] In addition, the initiation of long-term therapy for hyperuricemia is important for patients who have



*Interpretation of the serum urate level in urate deposition disease (gout)
Normal
Lifestyle guidance
Drug therapy should be considered if patient has comorbidities, including ischemic heart disease, diabetes, and/or metabolic syndrome
Drug therapy is advisory

FIGURE 1 Definition of hyperuricemia.