Second-to-fourth Digit Ratio in Systemic Lupus Erythematosus

Kentaro Doe, Kazuhisa Nozawa, Takuya Hirai, Hiroshi Tsushima, Eri Hayashi, Kaori Hiruma, Seiichiro Ando, Soichiro Nakano, Takayuki Kon, Hirofumi Amano, Ken Yamaji, Naoto Tamura, and Yoshinari Takasaki

ABSTRACT. ***Objective.*** Systemic lupus erythematosus (SLE) occurs predominantly in women, and sex hormones play an important role in SLE. Variation in the second-to-fourth digit ratio (2D4D ratio) is attributed to sex hormone exposure. Therefore, we evaluated the relationship between sex hormones and SLE by measuring 2D4D ratios.

Methods. We measured 2D4D ratios in 100 patients with SLE and 200 normal healthy controls (NHC).

Results. Patients with SLE had a lower 2D4D ratio than NHC.

Conclusion. Our study suggests that patients with SLE have experienced high prenatal testosterone and low prenatal estrogen. To our knowledge, this is the first study evaluating the association between 2D4D ratio and SLE. (J Rheumatol First Release March 1 2015; doi:10.3899/jrheum.140974)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS SEX HORMONE DIGIT RATIO 2D4D

In human hands, the relative lengths of index and ring fingers differ between men and women, such that men have a lower second-to-fourth digit ratio (2D4D ratio) than women. Baker reported this characteristic in 1888[1]; however, the reason for this difference was unknown at that time. In 1998, Manning, *et al* reported that the 2D4D ratio was linked to sex hormones[2]. Many reports about the 2D4D ratio have been published since then.

The 2D4D ratio is considered stable over time[3]. Interestingly, a low 2D4D ratio may reflect prenatal exposure to high testosterone and low estrogen levels[2]. Moreover, 2D4D ratio depends on the androgen receptors and estrogen receptors situated in the index and ring fingers[4].

Accumulating reports have indicated an association between the 2D4D ratio and the etiology of sex-biased diseases, including Klinefelter syndrome[5], schizophrenia[6], amyotrophic lateral sclerosis[7], myocardial infarctions[8], gastric cancer[9], prostate cancer[10], breast cancer[11], and oral squamous cell carcinoma[12].

From the Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, Tokyo, Japan.

K. Doe, MD, PhD; K. Nozawa, MD, PhD; T. Hirai, MD; H. Tsushima, MD; E. Hayashi, MD; K. Hiruma, MD; S. Ando, MD, PhD; S. Nakano, MD, PhD; T. Kon, MD, PhD; H. Amano, MD, PhD; K. Yamaji, MD, PhD; N. Tamura, MD, PhD; Y. Takasaki, MD, PhD, Professor, Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine.

Address correspondence to Dr. K. Doe, Department of Internal Medicine and Rheumatology, Juntendo University Faculty of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan.
E-mail: kdoe@juntendo.ac.jp

Accepted for publication January 9, 2015.

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that affects multiple organs. The etiology of SLE is still unknown, but SLE occurs predominantly in women, and sex hormones are believed to play an important role in the pathogenesis of this disease. Patients with SLE are reported to have high estrogen levels[13], and 17β-estradiol (E2) increases the production of immunoglobulin G (IgG) and anti-dsDNA antibodies from peripheral blood mononuclear cells (PBMC) in patients with SLE[14]. However, to date, there are no reports concerning the 2D4D ratio in patients with SLE or other connective tissue diseases. Therefore, we conducted this study to investigate the association between the 2D4D ratio and the etiology of SLE disease onset.

MATERIALS AND METHODS

Our study was approved by our local ethics committee in Juntendo University. Ambulatory patients with SLE were recruited at the Juntendo University hospital and its satellite hospitals, and these patients provided informed consent. All patients fulfilled the American College of Rheumatology criteria for SLE[15]. The normal healthy controls (NHC) were matched as closely as possible for age and sex, and they lacked any family history of autoimmune diseases. A total of 100 patients with SLE (50 men, 50 women) and 200 NHC (100 men, 100 women) participated in the present study. The samples were divided into 4 groups: male SLE group (SLE-M), female SLE group (SLE-W), male NHC group (NHC-M), and female NHC group (NHC-W). A digital camera was used to collect the images of both hands with a cross-section sheet, and digital length was measured from the proximal crease of the digit to the tip using the measurement tool in Adobe Photoshop (Adobe Systems Inc.). The lengths of the index and ring fingers were measured 3 times, and the average was used. The 2D4D ratio was calculated as the length of the index finger divided by that of the ring finger. The 2D4D ratios in both the right and left hands were analyzed. Statistical analysis was performed in the 4 groups

using the Mann-Whitney U test, and to investigate the association between the 2D4D ratio and SLE, simple and multivariate analyses were used. Intraclass correlation (ICC) of the repeated measures of the 2D4D ratio was performed to investigate the repeatability. A p value < 0.05 was considered statistically significant.

RESULTS

Three hundred images of the subjects were collected (SLE-M: 50, SLE-W: 50, NHC-M: 100, NHC-W: 100). The mean ± SD age (yrs) was 41.16 ± 13.93, 42.44 ± 14.58, 38.36 ± 8.37, and 31.46 ± 8.69 in the SLE-M, SLE-W, NHC-M, and NHC-W groups, respectively. ICC was 0.989, 0.989, 0.991, and 0.990 for the 2D in the right and left hands and the 4D in the right and left hands, respectively. This indicated strong similarity and high reliability in our measurements. The calculated 2D4D ratios for the 4 groups are shown in Table 1. Generally, the 2D4D ratio is believed to be lower in men than in women. As expected, our data indicated that the 2D4D ratio in the NHC-W group was significantly higher than that of the NHC-M group on both the right ($p = 0.0051$) and left hands ($p = 0.0024$). Interestingly, when evaluating the right hand, the 2D4D ratio in the SLE-M group was significantly lower than that of the NHC-M ($p < 0.0001$) and NHC-W groups ($p < 0.0001$); however, no significant difference was found between the SLE-M group and the NHC-M when evaluating the left hand ($p = 0.3929$). In addition to the SLE-M group, the 2D4D ratio in the SLE-W group was significantly lower than that in the NHC-W group when evaluating both the right and left hands ($p = 0.014$ and 0.0179, respectively). The results of simple and multivariate regression analyses are shown in Table 2. For the right hand, the 2D4D ratios of the SLE groups were statistically significantly lower when compared to that of NHC groups (β –0.025, 95% CI –0.035 to –0.015). Coefficient (β) of the SLE groups remained significantly lower even after adjusting for sex (β –0.025, 95% CI –0.034 to –0.015). For the left hand, however, significant difference was not observed between the SLE and NHC groups.

DISCUSSION

Manning, *et al* reported that the 2D4D ratio is associated with sex hormones, and that a lower 2D4D ratio reflects a high exposure of prenatal serum to testosterone and a low exposure to estrogen[2]. Thereafter, several papers have reported on the 2D4D ratio in sex-biased diseases[5,6,7,8,9,10,11,12]. However, to our knowledge, there have been no reports concerning the 2D4D ratio in connective tissue diseases, including SLE. We believe that this is the first report on the 2D4D ratio in patients with SLE.

In our present study, we clarified that both men and women with SLE have a lower 2D4D ratio than NHC of the same sex. Therefore, all patients with SLE are expected to have been exposed to high testosterone and low estrogen levels at birth. However, Folomeev, *et al* reported elevation of serum estrogen levels in patients with SLE[13]. Kanda, *et al* also reported that E2 increased the production of IgG, including anti-dsDNA antibodies in the PBMC of patients with SLE[14]. Moreover, on the contrary, testosterone has been reported to suppress anti-dsDNA antibody production[16]. Roubinian, *et al* also reported that estrogen levels increased IgG anti-dsDNA antibody production and testosterone reduced the serum anti-DNA antibody level in SLE-prone (New Zealand black × New Zealand white) F1 mice[17]. These reports have indicated the protective effects of testosterone and the deleterious effects of estrogen in SLE. However, our data indicated that exposure to high levels of testosterone and low levels of estrogen in the prenatal period was associated with SLE pathogenesis. This contradiction was reported in myocardial infarction (MI). Men have greater rates of MI than women, and it was expected that the patients with MI have low 2D4D ratio. However, men with low 2D4D ratio were protected against early MI[8]. This contradiction may be explained by the hypothesis that the amount of change in the exposure to estrogen plays an important role in the etiology of SLE onset. Aromatase is a cytochrome P-450 enzyme that catalyzes the conversion of sex hormones from androgens to estrogens. Folomeev, *et al* reported an increase in aromatase activity in patients with SLE compared with that in control subjects, and the aromatase activity in patients with SLE was significantly and directly correlated with estrogen levels[13]. Greenstein, *et al* reported the efficacy of the aromatase inhibitor in female MRL/MP-lpr/lpr mice with lupus nephritis[18]. The hypothesis suggested by our results is that patients with SLE have high levels of testosterone and low levels of estrogen in the early prenatal period. As a

Table 1. Comparison of the 2D4D ratios between the 4 groups.

Sex	Group	Right Hand			Left Hand		
		Mean	SD	95% CI	Mean	SD	95% CI
Males	NHC	0.947	0.044	0.938–0.956	0.958	0.042	0.950–0.967
	SLE	0.914*	0.041	0.902–0.925	0.955	0.043	0.943–0.968
Females	NHC	0.963	0.031	0.956–0.969	0.977	0.037	0.970–0.984
	SLE	0.946*	0.043	0.934–0.958	0.963*	0.046	0.950–0.976

* Statistically significant ($p < 0.05$) versus NHC. 2D4D ratio: second-to-fourth digit ratio; NHC: normal healthy controls; SLE: systemic lupus erythematosus.

Table 2. Association between the 2D4D ratio and SLE by sex and hand.

Hand	Group	Sex	Coefficient	95% CI	p	Coefficient Adjusted by Other	95% CI	p
Right	SLE negative		1	—	—	1	—	—
	SLE positive		–0.025	–0.035 to –0.015	< 0.001	–0.025	–0.034 to –0.015	< 0.001
		Males	1	—	—	1	—	—
		Females	0.021	0.012–0.030	< 0.001	0.021	0.012–0.030	< 0.001
Left	SLE negative		1	—	—	1	—	—
	SLE positive		–0.085	–0.019 to –0.015	0.096	–0.009	–0.019 to –0.0013	0.088
		Males	1	—	—	1	—	—
		Females	0.0151	0.0058–0.0244	< 0.01	0.015	0.0058–0.0245	< 0.01

2D4D ratio: second-to-fourth digit ratio; SLE: systemic lupus erythematosus.

result, an increase in aromatase activity leads to high estrogen levels, which triggers later SLE disease onset.

Our study had some limitations. First, the 4 groups were not age-matched. However, this may be irrelevant because the 2D4D ratio stabilizes over time[3]. Second, the sample size was small. Further comparative studies with larger patient groups are needed to confirm our findings. Third, the 2D4D ratio on the left hand was not significantly different between the SLE-M and NHC-M groups. However, this may be irrelevant because several studies evaluated 1 hand only[6,9,11,19]. Moreover, Zheng and Cohn reported that the 2D4D ratio on the right hand is more sensitive to prenatal sex hormones than that on the left hand[4].

We demonstrated that patients with SLE have a lower 2D4D ratio than NHC of the same sex. This is the first report, to our knowledge, concerning the association between the 2D4D ratio and the etiology of SLE. The amount of change in sex hormone levels during the fetal period may be important in the pathogenesis of SLE.

REFERENCES

1. Baker F. Anthropological notes on the human hand. Am Anthropol 1888;1:51-76.
2. Manning JT, Scutt D, Wilson J, Lewis-Jones DI. The ratio of 2nd to 4th digit length: a predictor of sperm numbers and concentrations of testosterone, luteinizing hormone and oestrogen. Hum Reprod 1998;13:3000-4.
3. Trivers R, Manning J, Jacobson A. A longitudinal study of digit ratio (2D:4D) and other finger ratios in Jamaican children. Horm Behav 2006;49:150-6.
4. Zheng Z, Cohn MJ. Developmental basis of sexually dimorphic digit ratios. Proc Natl Acad Sci U S A 2011;108:16289-94.
5. Manning JT, Kilduff LP, Trivers R. Digit ratio (2D:4D) in Klinefelter's syndrome. Andrology 2013;1:94-9.
6. Divakaran A, Narayanaswamy JC, Kalmady SV, Narayan V, Rao NP, Venkatasubramanian G. Family history correlates of digit ratio abnormalities in schizophrenia. Indian J Psychol Med 2012; 34:355-9.
7. Vivekananda U, Manjalay ZR, Ganesalingam J, Simms J, Shaw CE, Leigh PN, et al. Low index-to-ring finger length ratio in sporadic ALS supports prenatally defined motor neuronal vulnerability. J Neurol Neurosurg Psychiatry 2011;82:635-7.
8. Wu XL, Yang DY, Chai WH, Jin ML, Zhou XC, Peng L, et al. The ratio of second to fourth digit length (2D:4D) and coronary artery disease in a Han Chinese population. Int J Med Sci 2013; 10:1584-8.
9. Nicolás Hopp R, de Souza Lima NC, Filho JL, Filho MS, Lima CS, Jorge J. Digit ratio (2D:4D) is associated with gastric cancer. Early Hum Dev 2013;89:327-9.
10. Jung H, Kim KH, Yoon SJ, Kim TB. Second to fourth digit ratio: a predictor of prostate-specific antigen level and the presence of prostate cancer. BJU Int 2011;107:591-6.
11. Muller DC, Baglietto L, Manning JT, McLean C, Hopper JL, English DR, et al. Second to fourth digit ratio (2D:4D), breast cancer risk factors, and breast cancer risk: a prospective cohort study. Br J Cancer 2012;107:1631-6.
12. Nicolás Hopp R, Jorge J. Right hand digit ratio (2D:4D) is associated with oral cancer. Am J Hum Biol 2011;23:423-5.
13. Folomeev M, Dougados M, Beaune J, Kouyoumdjian JC, Nahoul K, Amor B, et al. Plasma sex hormones and aromatase activity in tissues of patients with systemic lupus erythematosus. Lupus 1992;1:191-5.
14. Kanda N, Tsuchida T, Tamaki K. Estrogen enhancement of anti-double-stranded DNA antibody and immunoglobulin G production in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Arthritis Rheum 1999; 42:328-37.
15. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
16. Kanda N, Tsuchida T, Tamaki K. Testosterone suppresses anti-DNA antibody production in peripheral blood mononuclear cells from patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:1703-11.
17. Roubinian J, Talal N, Siiteri PK, Sadakian JA. Sex hormone modulation of autoimmunity in NZB/NZW mice. Arthritis Rheum 1979;22:1162-9.
18. Greenstein BD, Dhaher YY, Bridges Ede F, Keser G, Khamashta MA, Etherington J, et al. Effects of an aromatase inhibitor on thymus and kidney and on oestrogen receptors in female MRL/MP-lpr/lpr mice. Lupus 1993;2:221-5.
19. Butovskaya ML, Vasilyev VA, Lazebny OE, Burkova VN, Kulikov AM, Mabulla A, et al. Aggression, digit ratio, and variation in the androgen receptor, serotonin transporter, and dopamine D4 receptor genes in African foragers: the Hadza. Behav Genet 2012;42:647-62.