

Low second to fourth digit ratio in Dupuytren disease

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Abstract

The ratio of the lengths of the second and fourth digits (2D:4D) has been described as reflecting endogenous prenatal androgen exposure. In general, 2D:4D is lower in men than in women and has potential as a biomarker or predictor for various diseases, athletic ability, and academic performance. Dupuytren disease has digital flexion contractures and is known to predominate in men, but the pathogenesis of the disease remains unclear. To clarify the relationships between Dupuytren disease and endogenous androgens, we performed a retrospective analysis of hand radiographs to investigate 2D:4D in Dupuytren disease. The study included male patients with Dupuytren disease (n = 22) and a control group (n = 18) of male patients with carpal tunnel syndrome. Only unaffected hands, without contractures or osteoarthritis, were evaluated for the purpose of radiographic assessment. The lengths of the phalanx and metacarpal bones in the second and fourth digits were measured by 2 independent observers who each performed 2 sets of measurements separated by a minimum 1-week interval. The 2D:4D was calculated separately for the phalanges and metacarpals, and a combined (phalanx + metacarpal) 2D:4D was also calculated. The reliability of the observer measurements was established using the intraclass correlation coefficient, and both the intra- and interobserver reliability showed excellent agreement. We found that compared with control group, the Dupuytren disease group had significantly lower phalanx and combined 2D:4D. These findings suggest that endogenous prenatal androgens could contribute to the development of Dupuytren disease, leading to its characteristic clinical presentation predominantly in men and affecting the ulnar rays.

Abbreviations: 2D:4D = ratio of the lengths of the second and fourth digit, 2D = the second digit, 2M = the length of metacarpal in index finger, 2P = the length of phalanges in index finger, 4D = the fourth digit, 4M = the length of metacarpal in ring finger, 4P = the length of phalanges in ring finger, BMI = body mass index, DD = Dupuytren disease, ICC = intraclass correlation coefficient.

Keywords: 2D:4D, androgen, digit ratio, Dupuytren disease, metacarpals, phalanges, radiographic assessment

1. Introduction

Dupuytren disease is a benign fibromatosis of the hands that is characterized by shortening of palmar fascia leading to

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progressive digital flexion contractures, especially of the ulnar side of the hand involving ring and little fingers.^[1] Although several risk factors, including genetic predisposition, smoking, diabetes, alcohol, epilepsy, and barbiturate use, have been implicated in the disease onset and progression, the pathogenesis of the Dupuytren disease remains unclear.^[2] Myofibroblasts differentiated from normal fibroblasts have been considered a cause of the flexion contractures. Because clinical investigations of Dupuytren disease have demonstrated a strong, unexplained predominance in men, with a male:female ratio of about 6:1 among Dupuytren disease patients,^[3] and a predominance in the ulnar rays, that is, the fourth and fifth digits,^[4] we developed a hypothesis that myofibroblast metabolism may be regulated by endogenous androgenic male hormones, which is also supported by the previous reports. Pagnotta et al^[5,6] have shown that the palmar fascia of Dupuytren disease had higher expression of the androgen receptors than in those without Dupuytren disease, and that cultured fibroblasts from patients with Dupuytren disease were significantly differentiated into myofibroblasts by stimulation with androgens.

Recently, the concept of studying the digit ratio has attracted renewed attention in various medical specialties,^[7-11] although the sexually dimorphic nature of this ratio has been reported for over 60 years.^[7] The evidence suggests that the ratio of the second and fourth digits (2D:4D) is a marker for endogenous sex hormone levels, for example the 2D:4D ratio decreases if the androgen level is high and estrogen level is low.^[8,9] The 2D:4D ratio is not only a biomarker for performance in various sports^[10,11] and academic ability^[12] but also, a putative predictor for cardiovascular

disease,^[13,14] oral^[15] and prostate cancer,^[16] alcohol dependency,^[17] and osteoarthritis.^[18,19] In general, 2D:4D is lower in men than in women,^[20] owing to the relatively longer fourth digits in men and the relatively longer second digits in women.

In the present study, to clarify the relationships between Dupuytren disease and androgens, we investigated the 2D:4D ratio as a marker of endogenous androgen sex hormone. The aim of the present study was to use radiographic assessment to determine whether lower 2D:4D ratio is associated with Dupuytren disease.

2. Methods

2.1. Participants

Between 2007 and 2015, patients with Dupuytren disease who underwent conservative or operative treatment at the Osaka City University Hospital were reviewed retrospectively. Patients with carpal tunnel syndrome who underwent operative treatment at the hospital during the same period were included as a control group, because they routinely undergo radiography of bilateral hands. Female patients were excluded from the study to prevent skewing of the results by their generally higher 2D:4D. Among the patients with Dupuytren disease, those with disease affecting both hands were excluded because of the difficulty of measuring digit length in fingers with contractures from hand radiographs. Patients with hand injury, Heberden node, Bouchard node, and rheumatoid arthritis were also excluded as potential confounders because these show radiographic abnormalities in carpometacarpal joints, metacarpophalangeal joints, and interphalangeal joints. Finally, 22 unaffected hands from patients with Dupuytren disease and 18 hands from patients in the control group were evaluated. The participants' demographic information was collected from their medical charts and included age, height, body weight, and body mass index (BMI) (kg/m²). This study was approved by the Osaka City University Ethics Committee. Informed, written consent was obtained from all participants.

2.2. Hand radiograph and measurement of digit length

Anteroposterior-view plain radiographs were taken of the hands prior to treatment, as follows: the participant was seated adjacent to the X-ray table with forearm and hand flat and prone on the table, with no lateral angulation at the wrist. The hand was centered on the cassette with fingers slightly spread but flat. The X-ray beam was centered on the third metacarpophalangeal joint. The exposure was set at 50 kV/2.8 mAs, with a 115-cm source-to-image distance. Each film was scanned and sent to OsiriX image processing software (Pixmeo, Geneva, Switzerland), which enabled straight-line measurements with an error of less than 0.01 mm.

According to a previous study that used radiographic assessment to determine 2D:4D,^[20] the following measurements were taken of the second and fourth digits of unaffected hands: the lengths of the phalanges were determined by measuring from the midpoint of the base of the proximal phalanx to the midpoint of the tip of the distal phalanx. The lengths of the metacarpals were determined by measuring from the midpoint of the base to the midpoint of the tip of the metacarpal. The combined lengths of the phalanges and metacarpals were calculated by adding the individual lengths (Fig. 1).

2.3. Intraobserver and interobserver reliability

Measurements of the digits were performed by 2 observers who were blinded to the participants' identity. Using the same

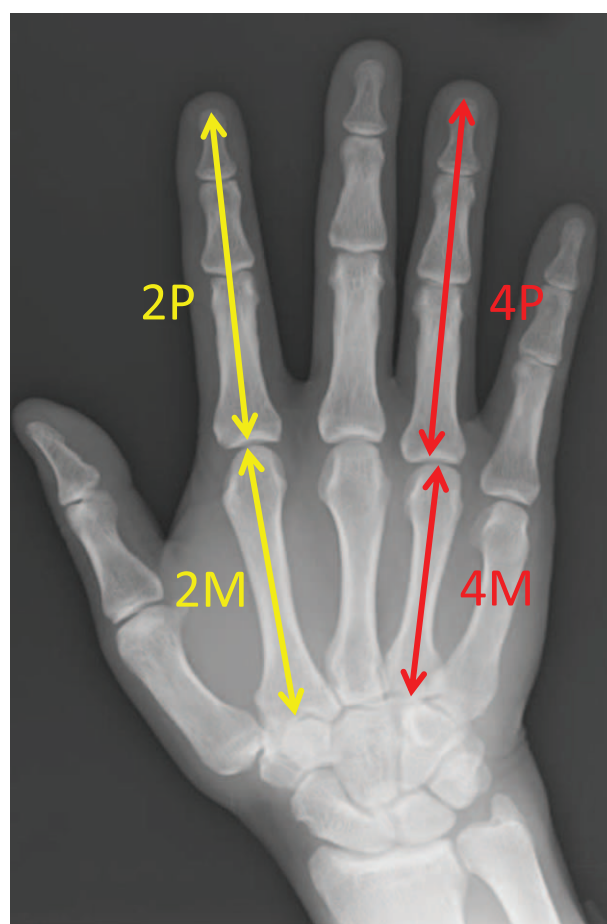


Figure 1. Measurement of the digit lengths. The length of phalanges (2P) and metacarpal (2M) in index finger. The length of phalanges (4P) and metacarpal (4M) in ring finger. The radiograph shows the length of the phalanx (2P) and metacarpal (2M) in the second digit, and the length of phalanx (4P) and metacarpal (4M) in the fourth digit.

radiographic measurement tool, each observer independently performed 2 sets of measurements, separated by a minimum 1-week interval. In consideration of possible intraobserver error, both observers performed 2 sets of measurements. Reliability was established using the intraclass correlation coefficient (ICC), which ranges from 0 (equivalent to chance agreement between observations) to 1 (perfect agreement). First intraobserver reliability was examined by comparing the mean 2D:4D measured by each observer. Next, interobserver reliability was examined by comparing the ratios measured by the first observer with those measured by the second observer. We used the 2D:4D values if the intraobserver reliability was “excellent,” that is, greater than 0.80, according to the guidelines described by Landis and Koch.^[21]

2.4. Statistical analysis

The mean and standard deviation were calculated for each measure after a normality test. Comparisons between the Dupuytren disease group and the control group were undertaken using an independent *t* test, using Prism software (Graph Pad Software Version 6.0, San Diego, CA). *P* values less than .05 (2-tailed) were considered significant. Post hoc power analyses were conducted using G*Power 3.1 software.^[22]

Table 1
Participant demographics.

	DD	Control	P value*
Number of patients	22	18	—
Number of right/left hands	12/10	12/6	—
Age, y	66.1±8.5	73.4±7.8	.01
Height, cm	168.3±5.4	163.7±6.3	.02
Weight, kg	65.6±9.3	64.3±12.5	.73
BMI, kg/m ²	23.1±2.5	23.9±3.8	.44

Data are expressed as mean ± standard deviation.

DD=Dupuytren disease, BMI=body mass index.

* Student *t* test.

3. Results

The demographics of the patients are shown in Table 1. The groups had a similar distribution of body weight, BMI, and number of right and left hands, although there were significant difference in age and height between the Dupuytren disease group and the control group.

The average lengths of the second and fourth digit phalanges and metacarpals, for both groups, are shown in Table 2. The average 2D:4D in the Dupuytren disease group was 0.900 ± 0.024 (phalanges), 1.157 ± 0.040 (metacarpals), and 1.001 ± 0.021 (combined). In the control group, the average 2D:4D was 0.917 ± 0.019 (phalanges), 1.172 ± 0.025 (metacarpals), and 1.017 ± 0.015 (combined) (Table 3). As shown in the Fig. 2, the phalanx and combined 2D:4D ratios in the Dupuytren disease group were significantly lower than those in the control group, with a post hoc analysis power of 0.780 and 0.988, respectively.

The ICCs for the phalanx and metacarpal measurements are shown in Table 4. The reliability analysis showed excellent intra- and interobserver agreement.

4. Discussion

The present study demonstrated that 2D:4D ratios, as evaluated from hand radiographs (with high intra- and interobserver reliability), were significantly lower in Dupuytren disease patients than in the control group. This suggests that Dupuytren disease might be associated with high endogenous androgen levels, consistent with its characteristic clinical presentation predominantly in males and affecting the ulnar rays (fourth and fifth digits).

With regard to the relationships between sex hormones and Dupuytren disease, Pagnotta et al^[5] showed the presence of androgen receptors associated with Dupuytren disease, both in the palmar fascia (especially, in the proliferative areas) and in cell cultures. Thereafter, they also reported that Dupuytren disease

Table 2
Lengths of phalanges and metacarpals.

Length (mm)	DD	Control	P value*
2D phalanges	78.6±2.9	79.6±4.2	.39
2D metacarpal	65.5±3.1	65.9±2.9	.74
2D combined	144.1±5.4	145.5±6.4	.49
4D phalanges	87.4±4.2	86.8±4.0	.62
4D metacarpal	56.7±2.9	56.2±2.4	.55
4D combined	144.1±6.7	142.9±5.4	.55

Data are expressed as mean ± standard deviation.

DD=Dupuytren disease, 2D=second digit, 4D=fourth digit.

* Student *t* test.

Table 3
2D:4D ratios in DD patients and controls.

Region	DD	Control	P value*	Power
Phalanges	0.900±0.024	0.917±0.019	.02	0.78
Metacarpal	1.157±0.040	1.172±0.025	.15	—
Combined	1.001±0.021	1.017±0.015	.01	0.99

The combined measure was calculated by adding the measurements of the phalanx and the metacarpal.

Data are expressed as mean ± standard deviation.

2D:4D=ratio of the lengths of the second and fourth digit, DD=Dupuytren disease.

* Student *t* test.

fibroblasts strongly expressed androgen receptors and that exposure of Dupuytren disease fibroblasts to androgen increased myofibroblast differentiation from fibroblasts.^[6] Conversely, estrogen and progesterone hormone receptors were not detected in palmar fascia in Dupuytren disease.^[23] Thus, fibroproliferative Dupuytren disease may be regulated by androgen, and androgen may play a role in the high male predominance of this disease. These results support our findings of low 2D:4D ratio in Dupuytren disease in the present study.

Several studies have suggested that fetal sex hormones, mainly androgens, are involved in sex-based 2D:4D variability and that 2D:4D does not change with aging.^[20] Zheng and Cohn^[24] discovered that in mice, 2D:4D is controlled by the balance of androgen to estrogen signaling during a narrow window of digit development and that androgen receptivity is higher in the fourth digit than in the second digit. The research also revealed that inactivation of androgen receptors decreases growth of the fourth digit, whereas inactivation of estrogen receptors increases growth of the fourth digit, leading to differential growth of the fourth digit in males and females. Thus, in males, the second digit is shorter than the fourth digit, but in females, the second digit is the same length or longer than the fourth digit. The finding of lower 2D:4D in Dupuytren disease in the present study suggests the high possibility that androgens contribute to the development of Dupuytren disease. The ulnar-side presentation in Dupuytren disease may also be linked with the localized higher androgen receptor expression in the fourth digit.

To date, 2D:4D has been recognized as an indicator for several diseases, including prostate cancer,^[16] oral cancer,^[15] myocardial infarction,^[14] alcohol dependency,^[17] and knee osteoarthritis.^[18,25] As well, 2D:4D has been associated with behavioral and physiological traits, such as athletic ability in rugby^[10] and surfing,^[11] and academic performance,^[12] however, no previous studies of 2D:4D have investigated its association with Dupuytren disease.

In the present study, comparison of the Dupuytren disease and control groups showed no significant difference in metacarpal 2D:4D but significant differences in the phalanx and combined (phalanx + metacarpal) 2D:4D. These results might be explained by the phalanx-specific effects of androgen such that androgen mainly affected phalangeal length,^[24] however, while most studies have measured the phalangeal 2D:4D,^[11,15,17] there is still controversy over which element of the finger—phalanges, metacarpals, or both—contributes to the variation in 2D:4D. The mean age of the control group was significantly higher than that of the Dupuytren disease group, but this is unlikely to have influenced the 2D:4D, as previous work has shown that 2D:4D is not associated with age.^[26,27] The mean height of the control group was significantly lower than that of the Dupuytren disease group, and did not influence the 2D:4D ratio, as previous reports

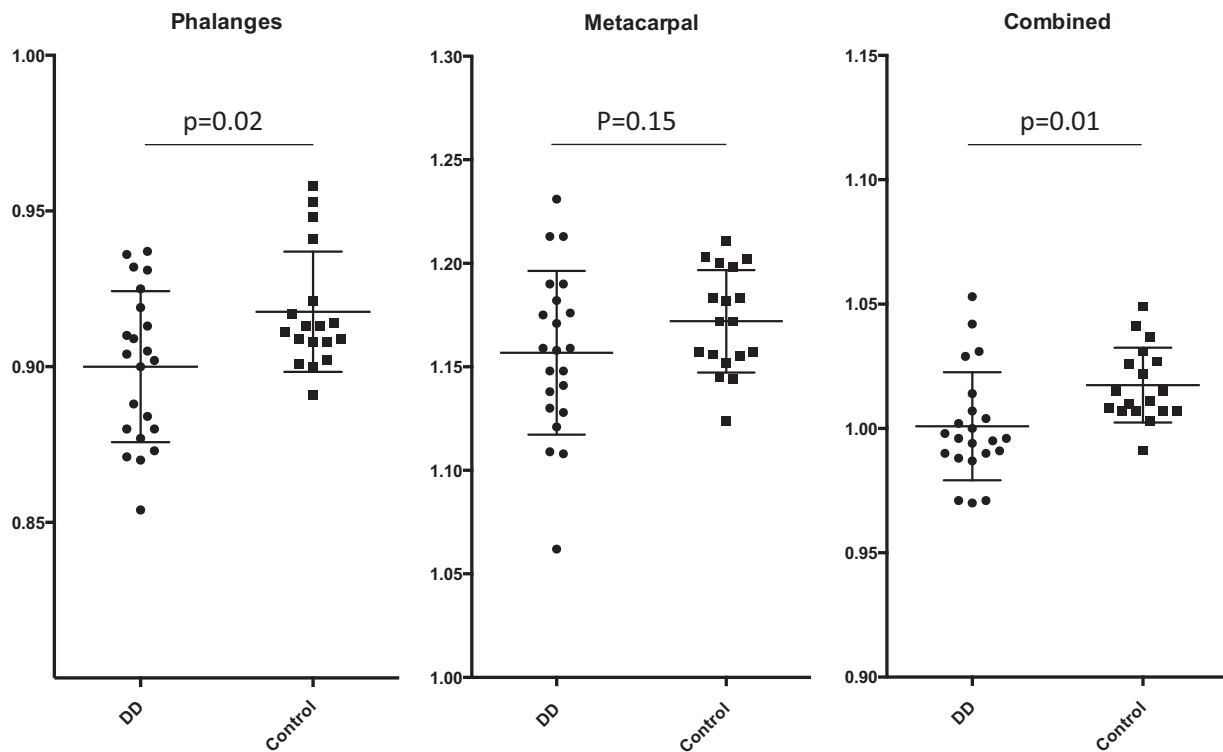


Figure 2. Comparison of the 2D:4D ratios between Dupuytren patients and Controls. Horizontal lines indicate mean with standard deviation. DD shows Dupuytren disease. 2D:4D= ratio of the lengths of the second and fourth digit, DD = Dupuytren disease. The combined measure was calculated by adding the measurements of the phalanx and the metacarpal.

have shown that the 2D:4D ratio is not associated with body height.^[28,29]

There are several limitations to our study. First, the sample size was relatively small. Second, the 2D:4D in Dupuytren disease was calculated from only unaffected hands (without contractures) for the purpose of the radiographic assessment, and it is possible measurements were different in the hand that was not measured; however, it has been reported that there is no difference in the 2D:4D ratio between the left and right hands^[20] and 2D:4D is not associated with handedness^[20] or age.^[26,27] Third, the control group included patients with carpal tunnel syndrome because the retrospective nature of the study necessitated the selection of patients who undertook hand radiograph for diagnosis. These subjects might not be considered a true standard. We think that healthy volunteers are best as a control group. However, it is difficult to perform radiography in this group because of radiation exposure and ethical concerns. Fourth, all the participants were Japanese males, which may affect the generalizability of our findings. Notably, it has been reported that the sex difference in 2D:4D is generally found across ethnic

and geographic groupings.^[30] Finally, the measurement of digit length was performed with radiograph, although consensus has not yet been reached regarding which measurement technique—direct measurement,^[8,31] indirect scanned image,^[32,33] or radiographic measurement^[34,35]—is most appropriate. Further studies should include a larger number of multinational participants and healthy controls and should use indirect as well as direct digit length measurement methods.

In conclusion, 2D:4D in patients with Dupuytren disease was significantly lower than that in the control group, indicating that endogenous prenatal androgens contributed to Dupuytren disease; for example, serum androgen levels might be used as a novel diagnosis parameter or severity marker for Dupuytren disease. Furthermore, an antiandrogenic agent might have the potential for conservative treatment of Dupuytren disease.

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Table 4

Interclass correlation coefficients for the length measurements.

	Intraobserver reliability		Interobserver reliability
	Observer 1	Observer 2	
2D phalanges	0.98	0.97	0.98
2D metacarpal	0.96	0.96	0.95
4D phalanges	0.90	0.99	0.97
4D metacarpal	0.96	0.95	0.95

2D=second digit, 4D=fourth digit.

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