



## Comparative Clinical and Pathomorphological Characteristics of Dupuytren's Contracture in Men and Women

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### Abstract

**Background.** The data available in the literature on the features of the clinical course and functional prognosis of Dupuytren's disease in women is contradictory, there are no data on comparative pathomorphological studies of palmar fibromatosis in men and women. **The aim of the study** was to identify possible differences in the clinical and pathomorphological characteristics of Dupuytren's disease in men and women. **Materials and Methods.** 228 cases of men and 39 women (6:1) who underwent fasciectomy in 2013–2019 period were analyzed. Histomorphometry of paraffin sections of the patient's palmar fascia specimens of 24 men and 24 women was performed. **Results.** Men ranged in age from 26 to 83, the median age is 3 years more in women ( $p < 0.001$ ), but the median age of Dupuytren's disease debut is 2 years less in women ( $p < 0.001$ ). The frequency of contractures of the 3<sup>rd</sup>–4<sup>th</sup> degree was 35.9% in the group of women and 65% in the group of men ( $p < 0.001$ ). In the group of women the frequency of both hands involvement is 15.2% higher, I–III fingers involvement is 8.7% higher, recurrent contracture is 11.1% higher ( $p < 0.1$ ). Histomorphometric analysis of the patient's palmar fascia specimens showed that women compared to men had 10.23% less adipose tissue ( $p < 0.001$ ), 7.87% less dense connective tissue ( $p < 0.05$ ), but the proportion of hyperplastic connective tissue was 20.31% higher. **Conclusion.** Dupuytren's disease is less common in women, than men. Women seek surgical treatment earlier than men. The tendency to functional limitations intensification and the risk of recurrence in women is associated with higher expression of hyperplastic changes in the fascial structures of the hand.

**Keywords:** Dupuytren's disease, palmar fibromatosis, gender dimorphism, gender differences.

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### Introduction

Dupuytren's contracture develops as a result of palmar fibromatosis (PF) — palmar aponeurosis fibroproliferative lesion [1]. Progressive flexion deformity of the digits, which develops as a result of thickening and contractile shortening of fibromatosely altered bundles of palmar-digital fascial structures, progressively and irreversibly disrupts the hand func-

tional capabilities [2]. Despite a wide range of conservative, minimally invasive and radical surgical treatment methods, its generally accepted tactics have not been developed, and we are far from solving the problem of postoperative complications and relapses [3]. Previously, Dupuytren's contracture was an insignificant part among patients of orthopedic and traumatology departments with hand deformities

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[4], but now the prevalence of the disease is increasing worldwide [5].

Alcohol dependence and hand injury predominate among the risk factors. The most common comorbidity is considered diabetes mellitus, epilepsy, hypertension, hyperlipidemia and gout [6]. Elderly age and male gender increase the likelihood of developing key pathophysiological mechanisms of Dupuytren's disease—vasoconstriction [7, 8], microangiopathy, tissue ischemia and free radical oxidation, since alcohol dependence and extreme smoking are more common in men [9]. In comparison with normal fascial structures, Dupuytren's contracture revealed an increased expression of androgen receptors in myofibroblasts of palmar aponeurosis; patients fibroblasts cultured in vitro differentiated into myofibroblasts when stimulated with androgens [10, 11], which can also explain the higher incidence of the disease in men.

In Europe, the ratio of men and women with Dupuytren's disease is 7:1 [12], and in the USA it is much lower—1.7:1 and reaches 1:1 in older age categories [13]. Information about the features of the clinical course and outcomes of surgical treatment of Dupuytren's contracture in women is contradictory. According to S. Stahl and E. Calif, women have less pronounced contracture at the time of surgery than men; the disease develops more slowly, and after surgery, all women manage to get good results [14]. According to N. Ferry et al., the prognosis of the Dupuytren's disease outcome for women is worse, since they often develop complex regional pain syndrome and do not achieve correction of the proximal interphalangeal joint contracture [15]. However, repeated operations for Dupuytren's contracture are more often performed in men, and the authors associate younger age at the time of the first operation with more frequent relapses [16]. Evidence has been obtained that the histological stage of the disease is an independent factor of relapse [17]. However, in the available literature, we have not found information

about the pathomorphological features of PF in men and women. The relevance of comparative studies of gender-related differences in the clinical course and pathomorphological characteristics of diseases, including PF, is determined by the needs of prognostic individually oriented medicine.

*The aim of the study was to identify possible differences in the clinical and pathomorphological characteristics of Dupuytren's contracture in men and women.*

## Material and Methods

### Research design

Design: a single-center retrospective observational study.

267 medical records of patients operated for Dupuytren's contracture in 2013–2019 at the National Medical Research Center of Traumatology and Orthopedics named after acad. G. A. Ilizarov were analyzed, of which 228 men and 39 women (6:1).

*The inclusion criteria* are clinically pronounced and histologically confirmed PF.

The exclusion criteria are hand injuries and multiple injuries in the anamnesis.

The comparative analysis of medical and statistical characteristics took into account the age at the time of surgery, the percentage of patients with the onset of PF at the age of less than 50 years, body mass index (BMI), the duration of PF (the number of years since the first symptoms), the frequency of both hands involvement, the degree of Dupuytren's contracture according to the R. Tubiana classification [18], the frequency of the I–III fingers lesions and the frequency of follow-up for contracture recurrence.

### Research technique

The surgical material obtained during open fasciectomy was immersed in a 4% formalin solution, the tissue samples cut out after 1–3 days were poured into paraffin. Longitudinal and transverse sections of aponeurosis were made on the Reichert mi-

crotome (Austria), stained with hematoxylin and eosin, picrofuxin according to Van Gieson and the Masson tricolor method. Full-color images of histological sections were obtained using an AxioScope.A1 microscope (Carl Zeiss MicroImaging GmbH, Germany) equipped with an AxioCam digital camera. For comparative analysis of the palmar aponeurosis tissue composition, equal-sized samples were formed ( $n = 24$ ): from the group of women — by random selection, from the group of men, patients operated in the same time period, comparable to women of the age range, were selected. At least 30 digital images of visual fields were obtained from each clinical case with an instrumental magnification of 200. Morphometry was performed using PhotoFiltre and "Video Test Master-Morphology, 4.0" programs. The quantitative ratio of palmar aponeurosis histostructural components was determined by the method of point-counting planimetry: blood vessels, adipose connective tissue, loose connective tissue, dense connective tissue and hyper-

plastic connective tissue according to the criteria set out by R. F. Warren [19].

### Statistical analysis

Statistical processing of quantitative data was carried out in Microsoft Excel spreadsheets using the Attestat program (version 9.3.1). Hypotheses about the normality of the distribution were tested according to the Shapiro – Wilk and Kolmogorov criteria. Since the hypothesis of normality was rejected for some selections, the tabular data are presented in the form of medians and quartiles-Me (Q1; Q3). To test hypotheses about the differences between the compared groups, the Mann–Whitney criterion was used, the Wald–Wolfowitz series criterion and Barnard's exact criterion.

### Results

In the groups of patients operated for Dupuytren's contracture, the age of men ranged from 26 to 83 years, the age of women—from 48 to 75 years, the median age was 3 years higher in women ( $p < 0.001$ ) (Table 1).

Table 1

Data of patients with Dupuytren`s disease.

Parameter	Women ( $n = 39$ )	Men ( $n = 228$ )	p
Age at the time of surgery, years (Me (Q1÷Q3))	62 (55÷65)	59 (56÷64)	0,00 <sup>1</sup>
BMI	27,8 (24,5÷32,5)	27,6 (23,3÷29,4)	0,42 <sup>1</sup>
Percentage of patients younger than 50 years	23,1	41,4	0,07 <sup>2</sup>
Dupuytren`s disease duration, years (Me (Q1÷Q3))	5 (3÷10)	7 (3÷10)	0,00 <sup>1</sup>
Degree of contracture (Me (Q1÷ Q3))	2 (2÷3)	3 (2÷3)	0,03 <sup>1</sup>
Percentage of patients with 3-4 <sup>th</sup> degrees of contracture	35,9	65	0,00 <sup>2</sup>
Both hands involvement, %	61,5	46,3	0,08 <sup>2</sup>
I–III fingers involvement, %	22,8	14,1	0,07 <sup>2</sup>
Frequency of known contracture recurrences, %	17,9	6,8	0,07 <sup>2</sup>

<sup>1</sup> – the Wald-Wolfowitz run test; <sup>2</sup> – Barnard`s test.

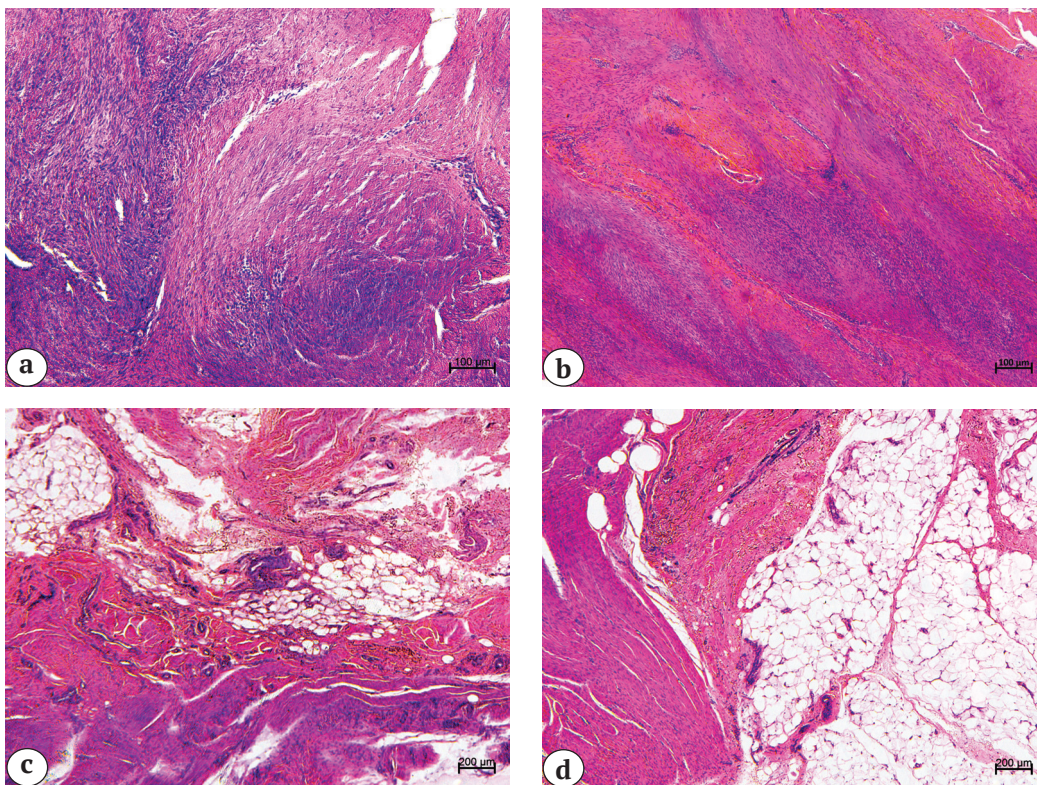
The proportion of patients with the debut of PF at the age of less than 50 years was 18% higher in the group of men (the difference at the level of statistical trend is  $p < 0.1$ ). The median age of PF was 2 years less in the group of women ( $p < 0.001$ ), but the median degree of contracture in women was also less (2 vs. 3,  $p < 0.05$ ). The frequency of the 3rd-4th degree contractures was 29% higher in the men group. In the women group, the frequency of both hands involvement was 15.2% higher, the frequency of the I-III fingers lesions was 8.7% higher, and the frequency of follow-up for recurrent contracture was 11.1% higher ( $p < 0.1$ ).

According to the medical records, women had no bad habits in the anamnesis, and men in isolated cases had alcohol dependence and extreme smoking (more than a pack of cigarettes a day) — in 7.79%. The most com-

mon professions in the women group were accountant and teacher, in the men group — driver.

The age-stratified selections from the groups of women and men formed for histomorphometric analysis were comparable in terms of the PF duration, as well as the Dupuytren's contracture degree (Table 2).

Microscopic examination of the surgical material in both groups revealed fibromatous nodes and cords, areas of node-to-cords transformation, greater or lesser fibrous replacement of the hypodermis adipose tissue (Fig. 1). Histomorphometric analysis of the surgical material tissue composition showed that women had 10.23% less adipose tissue ( $p < 0.001$ ), 7.87% less dense connective tissue ( $p < 0.05$ ), but the proportion of hyperplastic connective tissue was 20.31% greater (Table 3).



**Figure 1.** Photomicrographs showing specimens from patients with Dupuytren's disease: a, c women, b, d — men; a — fibromatous nodes; b — adjacent to fibromatous node section of the hypodermis, septate dense connective tissue; c — conversion fibromatous nodes in bands of dense connective tissue; d — fibromatous bands near the border with the hypodermis.

Stained with hematoxylin and eosin. Magnification x200

Table 2

**Age, duration of Dupuytren`s disease and degree of contracture in the groups of patients formed for histomorphometric analysis**

No	Age, years		Duration, years		Degree of contracture	
	Women	Men	Women	Men	Women	Men
1	43	45	15	5	3	3
2	47	45	5	5	3	3
3	48	48	3	6	2	2
4	53	48	3	3	2	3
5	54	48	4	2	2	3
6	55	50	5	10	2	3
7	55	52	3	2	3	4
8	55	55	10	2	3	2
9	56	56	18	2	2	2
10	57	58	3	5	2	3
11	60	59	4	10	2	3
12	60	60	5	1	2	2
13	61	60	5	10	2	2
14	62	60	8	15	3	3
15	63	61	1	5	3	3
16	64	62	7	3	4	2
17	64	63	15	4	4	2
18	67	63	5	17	1	3
19	67	64	10	10	3	2
20	69	71	3	5	3	3
21	69	73	7	0,5	3	2
22	74	76	20	10	3	3
23	75	76	10	15	2	3
24	78	77	2,5	7	3	4
p*	0,64		0,63		0,59	

\* — Mann-Whitney U test.

Table 3

**Histological analysis of altered palmar fascia specimens, Me (Q1÷Q3)**

Tissue type, %	Women (n = 24)	Men (n = 24)	p Mann-Whitney U test
Adipose tissue	19,39 (14,22÷26,63)	29,62 (19,53÷34,44)	0,00
Dense connective tissue	34,20 (21,48÷40,68)	42,07 (30,42÷52,88)	0,04
Hyperplastic connective tissue	32,90 (23,44÷ 40,18)	12,59 (3,51÷19,54)	0,00
Loose connective tissue	6,11 (4,81÷7,18)	8,63 (3,45÷11,76)	0,18
Blood vessels	6,92 (4,7÷8,4)	6,10 (3,49÷7,16)	0,25

## Discussion

The contradictory information available in the world literature about sex - related differences in Dupuytren's contracture is explained by the relative rarity of this disease in women. When analyzing large patients selections, the match of symptoms in men and women was postulated [20].

In our study, for the first time, a quantitative comparative analysis of sex-related differences in the clinical and pathomorphological characteristics of Dupuytren's contracture was carried out. The obtained results showed that at the time of surgery, women were statistically significantly older than men, which is probably due to a wider age peak of the onset of PF: in men it is 40-59 years old, in women it is 40-69 years old [21]. The BMI in women and men with Dupuytren's contracture did not have significant differences, which probably reflects the specifics of the disease, since it does not agree with the data of population studies on a higher BMI in women [22].

In the women group in our study, there was a tendency to a higher frequency of both hands involvement, a higher percentage of follow-up for relapses and more frequent involvement of the middle finger and the radial side fingers than in men. Contractures of both hands and I-III fingers are associated with the risk of recurrence [23]. In addition, they cause a more pronounced functional

deficit than with contracture of the elbow side fingers. This factor and, perhaps, a more cautious attitude to their health were the reason for earlier women requests for surgical help, as evidenced by significantly lower medians of the disease duration and the degree of contracture than in men.

At the same time, the studied selection has a large number of patients with the 3rd-4th degree contractures (almost 36%), which also does not correspond to the classical ideas about the benign "female type" of Dupuytren's disease [24].

The determination of the hyperplastic connective tissue percentage in the surgical material is more accurate than the expert assessment of its cellularity [25], which is applicable in quantitative comparative studies. High cellularity is characteristic of proliferative and fibrocellular histological types of PF according to the classification of J. J. Rombouts and co-authors [26], which are associated with earlier and more frequent recurrence than the third – fibrotic type [27]. Attempts are being made to predict the aggressive course of PF based on the results of immunohistochemical studies using the ki-67 proliferation marker and the myofibroblast marker  $\alpha$ -SMA ( $\alpha$ -smooth muscle actin) [28].

The difference in the content of hyperplastic tissue in men and women in the surgical material in our study fits with the data available in the literature on the sexual di-

morphism of proinflammatory cytokines in the aging process. In particular, the levels of the cytokine Il-6, which controls the proliferative activity of fibroblasts during wound healing and Dupuytren's disease [29], are maximum in men aged 50-61 years, and in women-at the age of 61-70 years [30].

### Limitations and prospects

The limitation of the performed study is its monocenter nature and the average selection size of women, however, the tendency to slightly more frequent recurrence in women than in men fits with the data of histological studies on a higher content of hyperplastic connective tissue in the women surgical material.

Further studies of gender (socio-psychological) and biological sex-related differences in the symptoms and results of Dupuytren's contracture treatment on large selections of patients are promising. Some factors of the pathogenesis of PF are modifiable, and this can be used to improve the protocols of complex treatment — for example, correction of the antioxidant status in the postmenopausal period [31].

### Conclusion

Dupuytren's contracture is much less common in women than in men. Women seek surgical help earlier than men. The statistical tendency to a more significant functional deficit and the risk of recurrence in women is associated with more pronounced hyperplastic changes in the fascial structures of the hand.

### Ethical expertise

The study was carried out in accordance with the ethical standards of the Helsinki Declaration of 1975, revised in 2013, approved by the local ethical committee (Protocol No. 2 (57) of 19.03.2018).

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