Epidemiology of Dupuytren disease unraveled

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4.5-year results of a prospective cohort study on disease course of primary Dupuytren disease

7

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ABSTRACT

Background

The exact natural course of Dupuytren disease is unclear. The primary aim of this study was to determine the long-term course of Dupuytren disease, in patients with different disease stages. A secondary aim was to identify factors that are associated with disease progression.

Methods

258 Dupuytren disease patients were included in this longitudinal cohort study. The follow-up period was 4.5 years, and measurements took place with a 6 months interval. In total, 16,340 observations were gathered. Disease extent (surface area) and contracture severity (TPED) were measured by physical examination, and demographic details were registered. Additionally, information on lifestyle factors, related diseases, and exposure to heavy manual work was gathered.
Subject-specific mixed-effects models were used to estimate the natural disease course in both outcomes (area and TPED) and to determine covariates associated with progression.

Results

Although on average Dupuytren disease was progressive in most fingers with regard to area (yearly increase ranging between 0.18 – 0.43 cm^2) and TPED (yearly increase ranging between -0.20 – 2.61^0), substantial numbers of participants did not experience progression (area: 2.4 – 26.2%, TPED: 1.8 – 65.8%). There were only two covariates that were strongly associated with disease progression, namely the presence of Ledderhose disease (area) and hospital population (TPED).

Conclusions

On the long-term, Dupuytren disease is progressive with regard to both area and TPED, but the increase in TPED is less pronounced. Ledderhose disease and population were covariates associated with progression. The majority of the clinical and anamnestic factors were not (consistently) associated with progression, suggesting that such factors have limited importance when predicting disease course.

INTRODUCTION

From a clinical point of view, it is often thought that Dupuytren disease is strongly progressive. This might be explained by the fact that a hospital population usually consists of patients with a more severe form of the disease. In the general population, the majority of cases have only a mild form of the disease, in which only nodules are present.[1] In such cases, it is probable that patients will not seek medical advice, since they have no complaints (yet). It might even be that they are unaware of having a mild form of Dupuytren disease. As such, it is likely that the hospital population is different from the general Dupuytren population. This assumption is further supported by the finding that there are also cases in which the disease is stable, or even in regression.[2] Precise knowledge about the disease course is important to gain insight in the development of the disease, to provide evidence-based patient information, and to facilitate the timing of treatment. More importantly, it might be possible to identify factors that predict disease progression.

There are a few studies in which the disease course was determined.[2-5] However, in two of these studies only two measurements were done.[2,3] In this way, it is only possible to determine whether a change over time has taken place, but it provides no information about the exact course of the disease. A third study described the results of surgical treatment compared with no treatment, with a follow-up of 5.5 years.[4] Data of the untreated controls can be considered as results on the natural disease course. Unfortunately, the sample size in this study was very small (47 hands were included in control group, unknown to how many participants they belong) and no statistical analyses have been done to describe the disease course. This limits the interpretability of the results. A fourth study is a prospective cohort study, in which progression over 1.5 years is clustered in groups of similar disease course profiles.[5] The short-term results of this study showed that Dupuytren disease was stable in the majority of the cases, but some experienced progression or even regression. Although a strong association was found between Tubiana stage at inclusion and change in disease extent, no other risk factors for disease progression were identified.

In the current paper, the long-term results of this prospective cohort study are presented. The following research questions are addressed: 1) What is the average and individual long-term course of Dupuytren disease, and 2) What factors are associated with disease course?

METHODS

Design

The design was a longitudinal prospective cohort study, in which measurements took place between June 2012 and January 2017 with an interval of 6 months. So, the follow-up period was 4.5 years and 10 measurements per participant were gathered in total.

Participants

A total of 452 adult patients who had primary (i.e. untreated) Dupuytren disease in one or both hands, were asked for participation. The participants were recruited from two sources: 1) from a random sample, stratified on age, of the general elderly population of the city of Groningen who were included in a previous study of our research group,[1] and 2) from Dupuytren patients who visited the outpatient clinic of the department of Plastic Surgery for a consult on Dupuytren disease. A sample size calculation was not possible, since no data is available from comparable studies on long-term disease course. We estimated that after 5 years, data of 200 participants would be sufficient for statistical analyses. Taking drop-out into account, we aimed to include at least 250 participants.

This study was reviewed and approved by the institutional ethics committee, and all participants gave written informed consent.

Outcome measures

The primary outcome measures were disease extent and severity of contracture. Disease extent was determined by physical examination of the hands, in which the nodules and cords were marked with a skin pencil. We used the surface area of nodules and cords measured with a tumorimeter, to quantify disease extent (see Chapter 5).[6] The area of nodules and cords in the same ray were summed to form a total area per finger. Contracture severity was determined by measuring the passive extension deficit (i.e. the flexion contracture) of each finger joint, using a goniometer. These extension deficits were summed to form the total passive extension deficit (TPED) per finger. TPED was not measured in the thumb, as Dupuytren cords in the thumb rarely lead to functional restraints. Contractures of cords in the first web space can lead to functional problems, but are not captured by measuring TPED.

We collected information on sex and age, and during all follow-up measurements we interviewed the participants about possible risk factors for Dupuytren disease progression, such as (past) exposure to vibration or heavy manual work during occupational or leisure activities, smoking and drinking habits, hand injuries, abnormal scarring, and familial occurrence of Dupuytren disease. Further, we asked the participants about the presence of diabetes mellitus, liver disease, epilepsy, Ledderhose disease, Peyronie disease, and general health. In case of doubt about the presence of Ledderhose disease, the feet were examined. The hands were also examined for presence of knuckle pads.

Procedures

Data of the first 1.5 years were gathered by the second author, while the first author gathered data during further measurements. An inter-observer agreement study was done to ensure reliability of the measurements (Chapter 5).[6] All measurements were done using exactly the same instruments.

Every 6 months, the participants visited the outpatient clinic of the Department of Plastic Surgery for this study. In case the participant was not able to visit the hospital, e.g. due to injuries or decreased health, the examiner visited the participant at home if possible. During the course of the study, a few participants refused to visit the hospital every 6 months. To prevent drop-out, they were asked to continue participation with a yearly visit.

Some participants received treatment during the course of the study. Data collection continued, but the data of the treated hand was excluded from the current analysis. Data from participants who were treated at both hands during the course of the study was also excluded from the current analysis.

Statistical Analysis

Characteristics of the participants were described using frequencies and percentages for count data, and with means and standard deviations for normally distributed continuous variables. For data that was not normally distributed, medians and interquartile ranges (IQR) were used.

The statistical analysis was applied to the surface area of nodules and cords, and to TPED separately. Furthermore, for each outcome the analysis was conducted per finger and it contained several steps.

The first step was to fit subject-specific time profiles for each individual using a mixed-effects model. The time profile was taken linear. In case the finger was affected by Dupuytren disease for the full follow-up period, the intercept and slope of the time profile were taken bivariate normally distributed, but when Dupuytren disease started somewhere during follow-up (thus after the start of the study), the intercept was taken zero until the moment when Dupuytren disease was detected, and the slope was considered random (for extensive explanation, see Appendix 7.1). The six parameter estimates of this model (parameter estimate for intercept and slope, three variance components, and one correlation coefficient) were reported, as well as the R^2 value that indicates how much variability in the observations is explained by the model.

The second step tried to select relevant covariates one by one before a more extensive model was possibly fitted. The same linear fixed-effects model was used as in the first step, but it was extended with one covariate. The disease progression (slope) could depend on the covariate, but not the baseline severity (intercept) since we were only interested in how progression would be influenced. This model was compared with the model in the first step using a likelihood ratio test at significance level alpha = 0.06 to test whether the covariate affected the area and TPED. If three or more fingers showed a significant likelihood ratio test (from the 8 fingers without the thumb), the covariate was selected for further analysis. Note that the probability of selecting three (or more) significances, when the covariate would not influence the disease progression, is equal to an overall type I error rate of 0.01. The covariates that were investigated one-by-one are sex, baseline age, smoking (never/ever), alcohol (never/ever), past hand injury (yes/no), manual labor (yes/no), manual hobbies (yes/no), Peyronie disease (yes/no), Ledderhose disease (yes/no), knuckle pads (yes/no), scars (yes/no), diabetes (yes/no), epilepsy (yes/no), liver disease (yes/no), first degree relatives with Dupuytren disease (yes/no), dominance (left/other), population (hospital/general (nonhospital)).

In the third step, the covariates that were selected in the second step were then put

in the linear mixed-effects model as in the second step, but now with all variables simultaneously. This was done only for progression (slope). The parameter estimates, their 95% confidence intervals, and p-values are being reported.

The selected model could easily handle missing values when they would be 'missing at random'. We decided not to impute missing data.

In all analysis we used maximum likelihood estimation. The statistical analysis of the linear mixed effects model was conducted with procedure NLMIXED of SAS institute, version 9.4. The trust region method was applied for the numerical method to maximize the likelihood with a maximum of 25 quadrature points.

RESULTS

Of the 452 eligible patients, 258 patients with primary Dupuytren disease in at least one hand, decided to participate. The number of participants and cases with available data during each measurement time are not equal (Table 1), since some participants were not able to attend each measurement time. The number of participants with available data is lower at T7-T9, as not all participants were included at the same time. From the 258 participants, 36 withdrew their consent during follow-up, 20 participants were excluded from the analyses due to bilateral treatment, 7 participants passed away, 6 were lost to follow-up, 5 were excluded since no Dupuytren disease was observed anymore in the untreated hand, and 2 were excluded by the researcher because they had cognitive decline making further participation unethical, leaving 182 participants at T9. Missing values in the active participants were scarce (< 3% from 16,340 observations).

The sample consisted of 163 men and 95 women, with a mean age of 66.4

Table 1. The number of participants and cases with available data presented for each measurement time.

	T0	T1	T2	T3	T4	T5	T6	T7	T8	T9
Follow up (yrs)	Start	0.5	1	1.5	2	2.5	3	3.5	4	4.5
Participants (n)	258	249	242	228	215	203	198	193	185	182
Available data (n)	258	244	237	223	202	182	185	172	168	155

N: number of subjects; T: measurement time.

(SD 10.4) at inclusion, with a range of 26 to 89 years. Of the 258 participants, 111 were recruited from the general population, and 147 from the hospital population. Those who could recall the age of onset (n = 198), reported a mean age of onset of 54.6 (SD 11.8) years.

The majority of the participants were smokers or former smokers, and for those, a median of 11 (IQR: 2 – 25) pack years was found. Among the participants who consumed alcohol, a median of 7 (IQR: 3 – 13) glasses per week was reported. Further details on the characteristics of the participants are presented in Table 2. The median time of follow-up was 52 months (IQR: 31 – 53).

Table 2. Characteristics of the cohort.

	N (%)	N missing (%)
Personal factors		
Hand dominance		0 (0.0)
Right	232 (89.9)	
Left	21 (8.1)	
Bimanual	5 (1.9)	
Intrinsic risk factors		
1st degree relative with DD	119 (46.1)	1 (0.4)
Diabetes	33 (12.8)	0 (0.0)
Liver disease	9 (3.5)	0 (0.0)
Epilepsy	3 (1.2)	0 (0.0)
Ledderhose disease	35 (13.6)	0 (0.0)
Peyronie disease (only in men)	15 (9.2)	0 (0.0)
Knuckle pads	84 (32.6)	0 (0.0)
Scarring		6 (2.3)
Normal	238 (92.2)	
Hypertrophic	10 (3.9)	
Keloid	4 (1.6)	
Extrinsic risk factors		
Heavy manual work	115 (44.6)	0 (0.0)
Hobbies with heavy manual work	114 (44.2)	43 (16.7)
Exposure to vibration	174 (67.4)	6 (2.3)
Smoking status		0 (0.0)
Current	28 (10.9)	
Former	161 (62.4)	
Never	69 (26.7)	
Alcohol consumption status		1 (0.4)
Current	195 (75.6)	
Former	31 (12.0)	
Never	31 (12.0)	
Hand injury	184 (71.3)	0 (0.0)

N: number; DD: Dupuytren disease

Natural course of Dupuytren disease – Area of nodules and cords

The parameter estimates of the linear mixed-effects model that does not yet include any of the covariates, are presented in Table 3 for area. The intercepts indicate the average area (disease extent) at the start of the study presented per finger, for all fingers affected with Dupuytren disease at a certain moment during the study. The parameter estimates of slope indicate the average increase in area (cm^2) per year. The results show that on average, the area of nodules and cords increases significantly over time, indicated by positive parameter estimates for slope. So, for example, the area of nodules and cords in the right index finger increases yearly with 0.33 cm^2 on average. This appears to be only a small increase, but a round shaped nodule with a diameter of 0.65 cm has a surface area of 0.33 cm^2. Furthermore, this concerns an increase per year, which means that in the right index finger, the surface area has increased on average with 1.49 cm^2 during the 4.5 year follow-up. This is equivalent to the formation of a new cord with a length of 3.0 cm and width of 0.50 cm. There were no large differences in increase in area between the left and right hand or between left and right fingers. The variance parameters show that there is a substantial amount of variation between participants, both in area at start of the study (variance intercept) and disease progression (variance slope). The area at start of the study does not seem to be strongly correlated to progression (correlation), except for the right thumb and left ring finger. There still seems to be a reasonable amount of unexplained variation in the data (variance residuals), but this is not really true since the model fit (R^2) ranged between 81.5 and 94.7%.

Natural course of Dupuytren disease – TPED

The parameter estimates in Table 4 can be interpreted in the same way as described for area in Table 3. The results show that overall, the TPED at the start of the study (intercept) was low, but increased over time. However, a decrease of TPED was also found in the right index finger, although statistical significance was not reached in the index fingers. The yearly average increases are small, ranging between -0.2 and 2.6°, while the variance of slope is large in the left ring and little finger. The model fit (R^2) ranged between 83.3 and 95.4%.

Table 3. Parameter estimates [95% confidence intervals] and model fit (R^2) of the subject specific model examining the surface area at start of the study (intercept) and course of area over time (slope), presented for both hands and fingers separately.

AREA		Fixed effects parameters		Variance-covariance parameters				
		Intercept	*Slope*	*Variance Intercept*	*Variance Slope*	*Correlation*	*Variance Residuals*	*R^2*
Right	Thumb	**1.47* [1.12; 1.82]**	**0.43* [0.34; 0.53]**	1.34 [0.72; 1.95]	0.13 [0.08; 0.19]	**0.71* [0.38; 1.00]**	0.36 [0.32; 0.41]	82.3
	Index	**1.16* [0.12; 2.21]**	**0.33* [0.20; 0.46]**	3.27 [1.00; 5.54]	0.12 [0.04; 0.19]	-0.46 [-1.00; 0.31]	0.18 [0.15; 0.21]	84.2
	Middle	**1.22* [1.01; 1.43]**	**0.21* [0.13; 0.29]**	0.73 [0.48; 0.98]	0.17 [0.12; 0.22]	0.26 [-0.12; 0.63]	0.18 [0.16; 0.20]	86.5
	Ring	**1.82* [1.63; 2.02]**	**0.18* [0.12; 0.23]**	1.27 [0.95; 1.59]	0.08 [0.05; 0.10]	0.13 [-0.11; 0.37]	0.25 [0.23; 0.27]	89.8
	Little	**1.55* [1.25; 1.85]**	**0.31* [0.23; 0.38]**	1.78 [1.23; 2.33]	0.15 [0.10; 0.19]	0.31 [-0.01; 0.63]	0.26 [0.23; 0.28]	89.6
Left	Thumb	**1.11* [0.88; 1.33]**	**0.40* [0.29; 0.51]**	0.45 [0.24; 0.65]	0.22 [0.14; 0.31]	0.22 [-0.36; 0.81]	0.24 [0.21; 0.27]	81.5
	Index	**1.65* [0.76: 2.55]**	**0.43* [0.26: 0.59]**	3.62 [1.17; 6.08]	0.16 [0.05; 0.28]	0.20 [-0.37; 0.76]	0.19 [0.15; 0.22]	94.7
	Middle	**1.21* [0.96; 1.46]**	**0.18* [0.10; 0.26]**	1.32 [0.89; 1.76]	0.14 [0.10; 0.19]	-0.30 [-0.63; 0.03]	0.26 [0.23; 0.28]	86.3
	Ring	**2.02* [1.74; 2.30]**	**0.27* [0.20; 0.34]**	2.57 [1.91; 3.23]	0.16 [0.11; 0.21]	**0.42* [0.17; 0.68]**	0.25 [0.23; 0.28]	91.9
	Little	**1.77* [1.37; 2.17]**	**0.32* [0.21; 0.44]**	3.35 [2.31; 4.39]	0.34 [0.23; 0.46]	-0.26 [-0.57; 0.05]	0.25 [0.23; 0.28]	93.2

*significant at $p < 0.05$

Table 4. Parameter estimates [95% confidence intervals] and model fit (R^2) of the subject specific model examining TPED at start of the study (intercept) and course of TPED over time (slope), presented for both hands and fingers separately.

TPED		Fixed effects parameters		Variance-covariance parameters				
		Intercept	*Slope*	*Variance Intercept*	*Variance Slope*	*Correlation*	*Variance Residual*	*R^2*
Right	Index	3.41 [-1.58; 8.39]	-0.20 [-0.77; 0.36]	153 [66.0; 239]	2.12 [0.64; 3.60]	**-0.91* [-1.0; -0.74]**	7.31 [6.19; 8.44]	83.3
	Middle	**2.50* [0.72; 4.27]**	**0.85* [0.27; 1.44]**	70.9 [47.7; 94.1]	8.79 [5.69; 11.9]	**0.63* [0.44; 0.81]**	7.49 [6.76; 8.23]	88.8
	Ring	**1.89* [0.36; 3.41]**	**2.03* [1.36; 2.71]**	83.2 [62.2; 104]	15.8 [10.1; 21.5]	**0.62* [0.46; 0.79]**	14.7 [13.4; 16.0]	88.9
	Little	**6.06* [1.64; 10.5]**	**1.07* [0.47; 1.67]**	465 [328; 601]	8.01 [4.33; 11.7]	0.11 [-0.23; 0.44]	20.9 [18.9; 23.0]	91.9
Left	Index	4.46 [-0.29; 9.21]	0.12 [-0.41; 0.66]	109 [39; 178]	1.59 [0.25; 2.94]	-0.38 [-0.79; 0.03]	2.29 [1.87; 2.72]	95.4
	Middle	**2.46* [0.73; 4.19]**	**0.61* [0.15; 1.08]**	73.2 [51.4; 95.0]	4.93 [3.00; 6.85]	-0.07 [-0.50; 0.36]	7.50 [6.73; 8.26]	84.2
	Ring	**3.11* [1.21; 5.01]**	**2.10* [1.20; 3.00]**	128 [96.6; 159]	30.2 [21.8; 38.6]	**0.44* [0.29; 0.59]**	13.7 [12.5; 14.9]	93.2
	Little	**8.24* [3.20; 13.3]**	**2.61* [1.46; 3.75]**	608 [430; 785]	34.8 [22.9; 46.8]	0.19 [-0.04; 0.43]	28.9 [26.1; 31.8]	94.0

*significant at $p < 0.05$

As we mentioned earlier, each individual had its own disease course profile. In Table 5 we have provided the percentage of participants who did not have a disease progression. These results are calculated for each finger and outcome separately. The percentage participants having regression varies between hands and fingers, although in the left middle fingers, almost a quarter of the participants experienced disease regression, measured as area. With respect to TPED, even 65% of the participants experienced disease regression in the right index finger. In the right thumb (area) and left ring finger (TPED), low percentages of regression were found.

Table 5. Percentage of participants having regression, presented for each finger and outcome separately.

			Area	TPED
		Total n	*% Negative slope*	*% Negative slope*
Right	Thumb	85	2.35	NA
	Index	49	6.12	65.3
	Middle	122	26.2	8.20
	Ring	164	14.6	2.44
	Little	133	16.4	6.02
Left	Thumb	96	8.33	NA
	Index	39	2.56	7.69
	Middle	134	25.4	5.22
	Ring	169	14.2	1.78
	Little	141	13.5	4.26

n: number; TPED: total passive extension deficit; NA: not applicable.

Factors associated with progression

In Table 6 we have listed the results from the selection of the single covariates influencing the disease progression (step 2 of the analyses). The reported 'Area' in the table indicates that the covariate has a significant influence on the outcome variable area of nodules and cords. The reported 'TPED' indicates that the covariate has a significant influence on the outcome variable TPED. So, for example, the covariate sex had a significant influence on area in the right index finger, and on TPED in the right ring finger. It is important to note that such findings might be due to chance. This is why we selected covariates for the multivariate model (step

3 of the analyses), only when the covariate was significantly associated with the outcome in at least three fingers. This was the case for Ledderhose disease, which seems to influence disease progression in four fingers on the outcome area. The same was found for population, which seems to influence disease progression in four fingers on the outcome TPED.

Table 6. Selection of single covariates with an effect on disease progression.

	Left				Right			
	Index	***Middle***	***Ring***	***Little***	***Index***	***Middle***	***Ring***	***Little***
Male sex					Area		TPED	
Baseline age							TPED	TPED
Smoking								
Alcohol consumption		Area			Area TPED			
Hand injury	Area TPED			TPED				
Heavy manual work	TPED		Area		Area			
Hobbies with heavy manual work							Area TPED	
Peyronie disease							TPED	TPED
Ledderhose disease	Area		Area		Area		Area TPED	TPED
Knuckle pads		Area					TPED	
Abnormal scarring				Area			TPED	
Diabetes								
Epilepsy		Area						
Liver disease				TPED		TPED		
First degree relatives with DD	Area							
Right dominance			TPED					TPED
Hospital population		TPED	TPED	TPED			Area TPED	

TPED: total passive extension deficit; DD: Dupuytren disease.

In Table 7, the parameter estimates of the effect of Ledderhose disease on progression of area (slope) are presented. Only the fingers for which Ledderhose disease was significant were reported. The second column of the table ('Constant') presents the slope of participants without Ledderhose disease. The positive parameter estimates in this column indicate that participants without Ledderhose disease had disease progression. The fourth column of the table ('Ledderhose disease') presents the influence of Ledderhose disease on the slope of area, or in other words, the influence of having Ledderhose disease on the disease course. To obtain the slope of participants with Ledderhose disease, this parameter estimate has to be added to the parameter estimate reported in the column 'Constant'. Note that the parameter estimate of Ledderhose disease in the left index finger is negative, indicating that participants with Ledderhose disease have less rapid disease progression in the left index finger, than those not suffering from Ledderhose disease. In the other fingers, participants with Ledderhose disease had more rapid progression than those without, as indicated by the positive parameter estimates for 'Constant' and 'Ledderhose disease'.

Table 7. Effect of Ledderhose disease on disease progression measured as area.

AREA	Disease progression			
	Constant	*p-value*	*Ledderhose disease* [a]	*p-value*
Left index	0.56 [0.34; 0.79]	< 0.001	-0.49 [-0.81; -0.16]	0.004
Left ring	0.25 [0.18; 0.32]	< 0.001	0.29 [0.08; 0.49]	0.007
Right index	0.27 [0.12; 0.42]	< 0.001	0.21 [0.04; 0.39]	0.019
Right ring	0.15 [0.10; 0.20]	< 0.001	0.19 [0.07; 0.31]	0.003

[a] Reference = no Ledderhose disease.

In Table 8, the parameter estimates of the effect of population on progression of TPED (slope) are presented. Only the fingers for which population was significant were reported. The interpretation of the parameter estimates is similar as explained above. The parameter estimates of population for progression of TPED are all positive, indicating that participants from the hospital population have more rapid disease progression than participants from the general population.

Table 8. Effect of population on disease progression measured as TPED.

TPED	Disease progression			
	Constant	*p-value*	*Population* [a]	*p-value*
Left middle	-0.07 [-0.67; 0.53]	0.823	1.38 [0.52; 2.24]	0.002
Left ring	0.45 [-0.72; 1.61]	0.449	3.37 [1.76; 4.98]	< 0.001
Left little	1.30 [-0.25; 2.84]	0.100	2.21 [0.37;4.06]	0.019
Right ring	1.04 [0.21; 1.86]	0.014	2.09 [0.96; 3.23]	< 0.001

[a] Reference = general population.
TPED: total passive extension deficit.

DISCUSSION

This study shows that overall, Dupuytren disease is progressive on the long term, with respect to disease extent (area). Progression in contracture severity (TPED) is also present, but less pronounced than for area. However, there were also cases that experienced disease regression in both area and TPED, since heterogeneity across participants was large. Furthermore, we demonstrated that Ledderhose disease and population are factors associated with progression, although we could not demonstrate this in all fingers. This study is the first step towards a progression prediction model, that might be used in clinical practice to quantify risk of progression.

There are no other studies known that describe disease course of Dupuytren disease based on prospectively gathered longitudinal data. The prospective nature of this study limits the chance of missing values, which is often a problem in retrospective database or patient file studies. Additionally, the follow-up measurements were done every 6 months, enabling a reliable estimation of the exact disease course profile. Our models were able to explain 81.5 to 94.7% of the variance for area, and 83.3 to 95.4% for TPED.

Another strength is that we used area of nodules and cords to measure disease extent. Disease extent is a parameter that can reflect disease progression apart from contracture severity measured as TPED. Although previous studies recorded outcomes such as “progression to bilateral disease” or “progression from nodules to cords”, or defined progression as a change in disease stage, none of these studies

quantified the disease extent.[2-4] By using area as outcome measure, we were able to follow the disease course also in participants with mild disease, without contractures.

Although measurement bias might have occurred when data collection was taken over by another observer, we performed an agreement study to determine whether the analyses required adjustment for this (Chapter 5).[6] Overall, high intraclass correlations were obtained, except for measurements of TPED in the left middle finger. So, it is unlikely that measurement bias played a large role in determining area and TPED. However, recall bias might have occurred in determining the risk factors, since this was gathered using an interview. To limit the influence of recall bias we interviewed the participants during each visit. Means and medians were used in the analyses, increasing the reliability of our measurements. Furthermore, changes in lifestyle or health status, that might influence the disease course, were identified early because of these repeated interviews. Despite this, it is possible that Peyronie disease has been underreported in our study, as physical examination of the genital area was not part of the data collection.

Drop-outs may form a problem in prospective studies, especially in longitudinal cohort studies with frequent follow-up measurements. In our study, this might have introduced selection bias, as it is possible that participants with mild Dupuytren disease were less motivated to continue long-term participation. As described in the methods, we had several strategies to prevent drop-out, but still a significant number of participants (n = 36) withdrew their consent during the study. However, the ratio of withdrawers in the general and hospital populations was comparable to the inclusion ratio (resp. 1:1.2 and 1:1.3), so selection bias seems unlikely. It can be argued to increase the follow-up interval of 6 months to, for instance, 12 months for continuation of this study, limiting the burden for the participants and to prevent further drop-out.

Our results, showing that Dupuytren disease is progressive in hospital patients with respect to TPED, are in line with the clinical point of view and in line with some previous studies.[2,3]

We were surprised by the finding that TPED only shows very small increases (or even a decrease, although not statistically significant) over time. However, it should be noted that the number of participants having flexion contractures during

the study, was limited. Furthermore, we used a linear time profile to estimate the course of TPED, and the reported estimates display the *average* increase over 4.5 years. Clinical experience shows that TPED is characterized by rapid increases, in which contractures can occur within a few weeks to months. This seems to be in conflict with our findings, but this is not necessarily the case, since the heterogeneity between participants was substantial. Although we thought of using other profiles than a linear time profile, such as an exponential time profile, visual inspection of the data did not show the necessity of using exponential models. Also, the fits of our models were high, indicating that the selected models do describe the data well, and limited improvement in model fit is possible with other time profiles. This might be explained by the fact that the start of an exponential growth curve approximates the linear relationship like we modeled it (Figure 1). Furthermore, the hands of many participants having rapid increase in TPED were excluded from the analysis as they received treatment to correct the contractures. So, in these cases, exponential growth could not be determined properly.

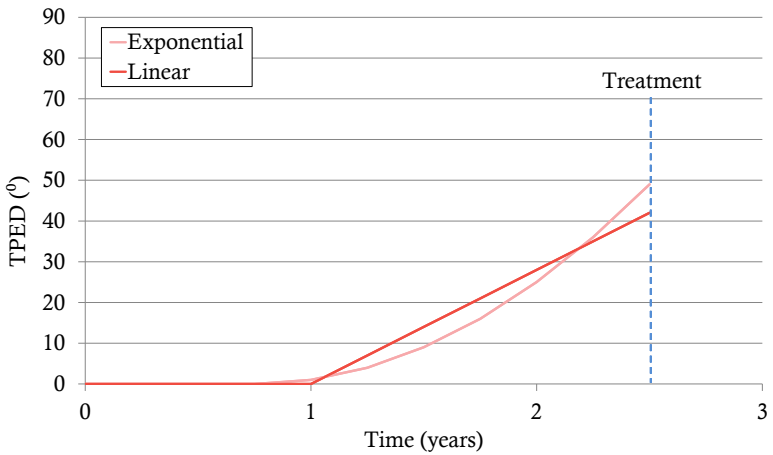

Figure 1. Representation of a linear model (that we used in our data-analyses) approximating an exponential model. The lines represent fictional data, only used as an example. At the time the total passive extension deficit (TPED) reached a certain threshold, the participant was treated and from this moment, data were excluded from the current analyses.

We also demonstrated that the presence of Ledderhose disease is associated with more rapid progression in area, and that participants from a hospital population have more rapid progression in TPED. So, there were only two covariates providing consistent results in multiple fingers.

From these results, it seems that the hospital and general populations are not the same. The question rises what exactly defines this difference between the two populations. When comparing these two populations on characteristics that we measured, there were some significant differences between the two groups (Appendix 7.2), although the covariates in which they differed were not identified as predictor, except for Ledderhose disease. It is possible that genetics may be part of the explanation, as patients having family members suffering from Dupuytren disease will probably be more aware of this disease, recognize it earlier and visit the hospital in an early stage. Such patients were included in our hospital population. However, having an affected first degree relative did not appear to influence progression in any of the outcomes. It might also be that the true number of affected relatives is underreported in the general population, as many participants answered the question "Does Dupuytren disease run in your family?" with "Not as far as I know". The fact that the majority of the participants did not have parents who are alive, might also contribute to underreporting. Future analyses including genetic information might provide insight in this assumption.

The interim analyses of this study could not identify an overall time profile for short-term disease course.[5] From the current results, it is clear that Dupuytren disease is progressive. Furthermore, in the interim analyses no covariates associated with disease progression were found, except for disease extent at baseline.[5] In the current analyses, we found two factors that were associated with progression. These differences in results can be explained by the longer follow-up time. In the current study, 4.5 years of data were used instead of 1.5 year follow-up data. It is likely that during the interim-analysis, the change over time was too small to be discriminated from measurement error. By continuing follow-up measurements (and consequently, increasing the amount of data), estimations of effects have become more precise. Furthermore, we used another approach for the statistical analyses, as the increased amount of data made the data-analysis much more complex. Especially the fact that many participants developed Dupuytren disease in a finger that was unaffected at

inclusion, is something that currently cannot be modeled with existing latent class models. Additionally, latent class modeling is not directly suitable to quantify the influence of factors associated with progression.

Nevertheless, it needs to be noted that the number of covariates that were associated with disease course, is very limited. This suggests that clinical variables like we collected do not seem to be important for predicting disease course. Furthermore, variables predicting disease extension or recurrence that were identified by previous studies, such as family history and male sex, were not associated with disease progression in our study.[7-9] As we cannot explain this discrepancy, apart from recall bias with respect to family history as explained before, new prospective studies should be done to evaluate this. The authors of a previous retrospective database study claim to have identified predictors for progression, namely bilateral disease, radial involvement, and little finger surgery.[7] We did not include these in our analyses, since it can be questioned whether these features are predictors for progression, or rather a consequence of progression. In our opinion, the suggested causal relation is the other way around: due to progression, patients are more likely to have bilateral disease, radial involvement and surgery in the little finger.

CONCLUSION

Due to the prospective nature of this study and the well-fitting statistical models, this study provides reliable conclusions about long-term natural disease course of Dupuytren disease. Overall, Dupuytren disease is progressive, but the speed of progression varies between participants from the hospital and general population, and between those with and without Ledderhose disease. An important finding is that the majority of the clinical and anamnestic characteristics that we collected were not associated with disease progression. This suggests that we should shift focus from clinical and anamnestic predictors to other predictors, such as genetic or cell biological factors. Since whole genome sequencing has become cheaper, it is relevant to evaluate whether patient-specific genetic risk profiles can predict progression. This will lay the foundations for personalized medicine, in which the treatment policy can be adapted to the specific risk and needs of a patient.

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Appendix 7.1. Explanation of mixed-effects models

The mixed-effects models that we used in our analyses, can be considered as an extension of linear regression analysis, with a random intercept and/or a random slope. In other words, it is linear regression analysis in which the intercept and slope of the line can vary between participants (Figure A). This means that for each individual participant a separate line is fit. In this way, the model is able to handle the data clustering that occurs as consequence of the repeated measures within participants. It is necessary to take this into account, as data that are derived within participants, such as repeated measures, cannot be considered as independent observations.

In our analyses, the intercept represents the area or TPED at start of the study (area and TPED were analyzed separately). The slope tells us something about disease course. A negative slope, which means that the line is descending, indicates regression, while a positive slope indicates progression. A slope that equals zero indicates no change over time, which is stability. In mixed-effects models, the intercept is usually taken random, and sometimes the slope is taken random too. However, in our dataset, there were many participants who did not have contractures in a finger until a certain moment in time. So, for these participants, we knew that the intercept was zero, until the moment that contracture occurred. In these cases, only the slope was considered random, while the intercept was set at zero until contracture occurred (Figure A, red solid line). The same principle was used for area: when Dupuytren disease occurred in a finger after start of the study, the intercept was taken zero until the moment that Dupuytren tissue was found in that finger.

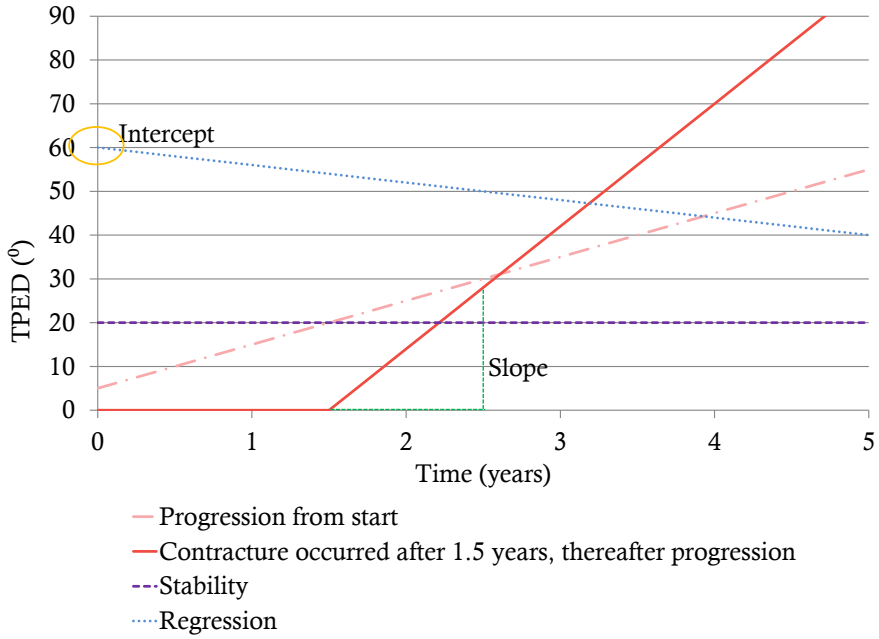

Figure A. Graphical representation of the principles behind mixed-effects models as used in our analyses. Each line represents the disease course of total passive extension deficit (TPED) in different participants, having different intercepts and slopes.

Appendix 7.2. Characteristics of participants from the general and hospital population. Reported p-values are from the X^2-test.

	General (n = 111)		Hospital (n = 147)		
	N (%)	*N missing (%)*	*N (%)*	*N missing (%)*	*p-value*
Personal factors					
Male sex	58 (52.3)	0 (0.0)	105 (71.4)	0 (0.0)	**0.002**
Hand dominance		0 (0.0)		0 (0.0)	
Right	103 (92.8)		130 (88.4)		
Left	7 (6.3)		14 (9.5)		0.480
Bimanual	1 (0.9)		3 (2.0)		
Intrinsic risk factors					
Age of onset ≤ 50	13 (17.8*)	38 (34.2)	42 (33.6*)	22 (15.0)	**0.017**
1st degree relative with DD	42 (37.8)	0 (0.0)	77 (52.7*)	1 (0.7)	**0.018**
Diabetes	14 (12.6)	0 (0.0)	19 (12.9)	0 (0.0)	0.941
Liver disease	2 (1.8)	0 (0.0)	7 (4.8)	0 (0.0)	0.200
Epilepsy	2 (1.8)	0 (0.0)	1 (0.7)	0 (0.0)	0.405
Ledderhose disease	10 (9.0)	0 (0.0)	25 (17.0)	0 (0.0)	0.063
Peyronie disease (only in men)	3 (5.2)	0 (0.0)	12 (11.4)	0 (0.0)	0.261
Knuckle pads	22 (19.8)	0 (0.0)	62 (42.2)	0 (0.0)	**< 0.001**
Scarring		5 (4.5)		1 (0.7)	
Normal	103 (92.8)		135 (91.8)		
Hypertrophic	2 (1.8)		8 (5.4)		0.083
Keloid	1 (0.9)		3 (2.9)		
Extrinsic risk factors					
Heavy manual work	49 (44.1)	0 (0.0)	66 (44.9)	0 (0.0)	0.904
Hobbies with heavy manual work	42 (37.8)	16 (14.4)	72 (49.0)	27 (18.4)	**0.021**

Appendix 7.2 (continued). Characteristics of participants from the general and hospital population. Reported p-values are from the X^2-test.

	General (n = 111)		Hospital (n = 147)		
	N (%)	*N missing (%)*	*N (%)*	*N missing (%)*	*p-value*
Exposure to vibration	67 (60.4)	3 (2.7)	107 (72.8)	3 (2.0)	**0.037**
Smoking status		0 (0.0)		0 (0.0)	
Current	12 (10.8)		16 (10.9)		
Former	70 (63.1)		91 (61.9)		0.979
Never	29 (26.1)		40 (27.2)		
Alcohol consumption status		1 (0.9)		0 (0.0)	
Current	69 (62.7*)		126 (85.7)		
Former	21 (18.9)		10 (6.8)		**< 0.001**
Never	20 (18.0)		11 (7.5)		
Hand injury	74 (66.7)	0 (0.0)	110 (74.8)	0 (0.0)	0.151

N: number; DD: Dupuytren disease
*Because of missing values, these percentages were calculated with respect to the number of complete cases (total participants minus number of participants with missing data).