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Published in:
The Journal of Hand Surgery

DOI:
[10.1016/j.jhsa.2015.10.027](https://doi.org/10.1016/j.jhsa.2015.10.027)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2016

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Citation for published version (APA):

Lanting, R., van den Heuvel, E. R., & Werker, P. M. N. (2016). Clusters in Short-term Disease Course in Participants With Primary Dupuytren Disease. *The Journal of Hand Surgery*, 41(3), 354-361. <https://doi.org/10.1016/j.jhsa.2015.10.027>

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Clusters in Short-term Disease Course in Participants With Primary Dupuytren Disease

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Disclosures for this Article

Editors

Jennifer Moriatis Wolf, MD, has no relevant conflicts of interest to disclose.

Authors

All authors of this journal-based CME activity have no relevant conflicts of interest to disclose. In the printed or PDF version of this article, author affiliations can be found at the bottom of the first page.

Planners

Jennifer Moriatis Wolf, MD, has no relevant conflicts of interest to disclose. The editorial and education staff involved with this journal-based CME activity has no relevant conflicts of interest to disclose.

Learning Objectives

Upon completion of this CME activity, the learner should achieve an understanding of:

- The stages of Dupuytren disease and their relationship to clinical presentation.
- The clinical behavior of Dupuytren disease over time.
- Potential risk factors for Dupuytren disease progression.

Deadline: Each examination purchased in 2016 must be completed by January 31, 2017, to be eligible for CME. A certificate will be issued upon completion of the activity. Estimated time to complete each JHS CME activity is up to one hour.

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Purpose The course of Dupuytren disease (DD) is thought to be progressive; however, the course differs for each patient. The purpose of this study was to study the rate and pattern of progression of DD.

Methods We prospectively analyzed the course of DD at intervals of 3 to 6 months in 247 Dutch participants with primary DD by measuring the surface area of nodules and cords and the total passive extension deficit. The association between surface area and Tubiana stage was tested with generalized estimating equations. Latent class models were used to study different clusters in changes regarding the course of the disease.

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Received for publication September 9, 2014; accepted in revised form October 7, 2015.

No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

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0363-5023/16/4103-0004\$36.00/0
<http://dx.doi.org/10.1016/j.jhsa.2015.10.027>

Results The variance in disease course between participants was large. Regarding the change in surface area (in all fingers) and total passive extension deficit (in the ring and little finger), different clusters were observed. Progression of disease was seen but there were also signs of stability and even regression. Patients with a smaller surface area at baseline were more likely to exhibit regression.

Conclusions This study showed that DD is not always progressive and that up to 75% of patients have a different short-term disease course, such as stability or even regression of disease. This should be taken into account when evaluating the effects of treatment for early-phase DD and in the design of future studies. Furthermore, this information may be useful when counseling patients. (*J Hand Surg Am.* 2016;41(3):354–361. Copyright © 2016 by the American Society for Surgery of the Hand. All rights reserved.)

Type of study/level of evidence Prognostic II.

Key words Disease course, disease progression, disease regression, Dupuytren contracture, Dupuytren disease.

DUPUYTREN DISEASE (DD) IS A CHRONIC fibromatosis of the palmar fascia of the hand and fingers. The etiology and pathogenesis have not been fully elucidated; however, the disease has a genetic origin.¹ The prevalence of DD in the general population of Western countries is estimated to be between 0.3% and 21.6%.² The disease is mainly diagnosed in white males of northern European descent, and prevalence rises with increasing age.^{3–6}

Clinically, DD starts with subcutaneous nodules in the palm. In a later stage, cords appear and shorten. Skin pits may occur and the fingers can be pulled into flexion. A flexion contracture can affect a single joint or adjacent joints of a finger, whereby the metacarpophalangeal joints and proximal interphalangeal joints are most frequently involved.

Some people will develop only small lumps that do not progress into cords and contractures; others will develop a severe contracture of the finger(s). A few authors have studied the clinical disease course of DD. Millesi⁷ diagnosed DD after a follow-up of 5 years in about 40% of patients (150 hands) who were previously unaffected. While studying 59 patients after an average follow-up of 8.7 years, Reilly et al⁸ found that in 51% of patients with nodules, the disease had progressed into cords. In the study of Gudmundsson et al,⁹ 35% of the 75 patients with DD had developed contractures or had been operated on after 18 years. Of the control group without DD (n = 101), 53% had developed clinical signs of DD in this period. These long-term studies suggest that the disease is progressive over time, although not in all patients. In these studies, there were only 2 moments of assessment; as a result, possible short-term fluctuations in the disease course were not defined.

Histological studies show that the course of development of DD can include periods of exacerbation and regression.^{7,10} Three stages have been described in DD: proliferative, involutinal, and residual. During these stages, the cells in nodules mature, collagen becomes aligned, and contraction occurs.¹⁰ Furthermore, stages in the development of DD can be repeated frequently, leading to periods of activity and inactivity.⁷ It is unknown how this histological process manifests clinically in patients with DD when focusing on short-term changes.

Thus, knowledge about the short-term course in patients is lacking. It is relevant to clarify this, for example, to determine the best moment in which to intervene and evaluate the effect of treatments for early-stage disease, such as radiotherapy or placement of an orthosis and/or use of stretching exercises. Therefore, the goal of this study was to scrutinize the short-term disease course of DD in participants with different stages of primary disease. To this aim, we introduced the surface area of nodules and cords as a new measurement to study the disease course in participants without an extension deficit and studied the association between this new measurement and the established classification of Tubiana et al.¹¹ Second, we hypothesized that several risk factors such as age, sex, and age of onset influence the course of disease. Thus, a secondary goal was to study the association between risk factors and the short-term course of the disease.

MATERIALS AND METHODS

Study design and measurements

The study was approved by the institutional review board and informed consent was obtained from each

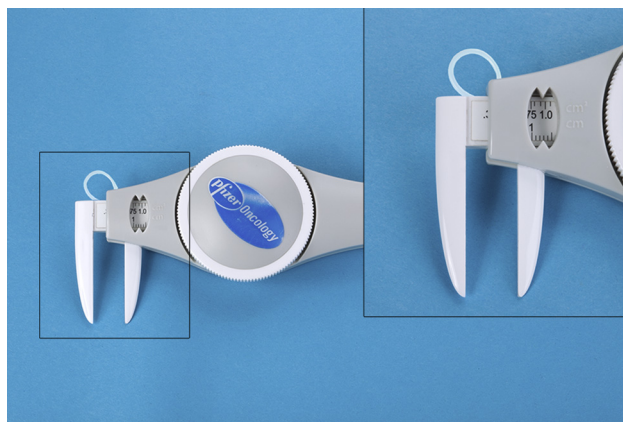


FIGURE 1: Tumorimeter with loop and caliper that was used in this study.

participant. Patients with primary DD in at least one hand, who participated in previous studies of ours on DD,^{1,6} were asked to participate in this prospective study. Of 449 eligible patients, 247 were willing to participate. In this study, we analyzed the results of 370 primary affected hands.

This study focused on the detailed investigation of changes in the hands of participants with DD, measured at maximum intervals of 6 months during a period of 20 months between June 2012 and January 2014. Participants with Tubiana stage 2 in one or more fingers were studied every 3 months because we hypothesized that they would experience more rapid progression. The first author, who was blinded to previous measurements, performed all measurements with the same set of instruments during all moments of follow-up. We introduced a way to study changes in patients without an extension deficit: namely, measurement of the surface area of nodules and cords in square centimeters with a tumorimeter^{12,13} (Pharma-Design, Inc, Warren, NJ) (Fig. 1). For round nodules, the loop of the tumorimeter was placed on an encircled nodule to determine the area in square centimeters. To determine the area of other-shaped nodules or cords, the length and width were measured with the calipers on the tumorimeter. The width was measured at the proximal, middle, and distal extents of the cord. Afterward, the area was calculated. Interobserver and intraobserver agreement on this measurement of area have been shown to be moderate (only the middle finger) to very good (intraclass correlation coefficient, 48%–99%).¹⁴ In addition to measurement of surface area, the passive extension deficit of each metacarpophalangeal, proximal interphalangeal, and/or distal interphalangeal joint was measured with a goniometer and added to form total passive extension

TABLE 1. Population Characteristics

	N (%)	95% Confidence Interval*
Participants	247	
Females	89 (36)	30–42
Family history of DD	100 (41)	34–47
Ectopic lesions		
Knuckle pads	58 (24)	18–30
Peyronie disease	18 (11)	7–17
Ledderhose disease	25 (10)	7–15
Disease		
Diabetes	32 (13)	9–18
Epilepsy	3 (1)	0–4
Liver disease	2 (1)	0–3
Hand trauma		
Hand injury	119 (48)	42–55
Manual labor	84 (34)	28–40
Exposure to vibration	84 (35)	29–41
Lifestyle factors		
Alcohol intake, glasses/wk		
0	42 (17)	12–22
1–5	87 (35)	30–42
6–10	43 (17)	13–23
11–15	39 (16)	12–21
16–20	20 (8)	5–12
>20	16 (7)	4–10
Smoking		
Never	73 (30)	24–36
>1 y stopped	140 (57)	50–63
<1 y stopped	3 (1)	0–4
Current	31 (13)	9–17

*Rounded to whole numbers.

deficit (TPED) but was recorded only when DD was present in this particular ray. Afterward, the severity of disease was categorized based on Tubiana classification.¹¹ This classification per ray uses the TPED of finger joints: stage 0 = no apparent lesions; stage N = nodules without extension deficit; stage 1 = 1° to 45°; stage 2 = 46° to 90°; stage 3 = 91° to 135°; and stage 4 = greater than 135° TPED.

We also interviewed participants about potential risk factors for DD (Table 1). Exposure to vibration included, for example, questions about playing tennis or field hockey and occupational exposure to vibrating tools. We also studied the presence of ectopic lesions by asking men about symptoms of

Peyronie disease, examining the hands for knuckle pads and the feet for Ledderhose disease when a participant had noticed plantar nodules.

Statistical analyses

Population characteristics were described by means and SDs or by proportions with 95% confidence intervals, which were calculated using the *F* distribution.¹⁵

To investigate whether our surface area measurement was related to other measures of disease severity, we studied whether there was an association between area and Tubiana stage at baseline. This was tested with generalized estimating equations using the cumulative logit link function, an independent working correlation matrix, the robust estimator, and the generalized score statistic.¹⁶ Hand and finger effects were considered within-subject variables in this analysis, so the results were applicable to all fingers of both hands.

To study the course of the disease, we used latent class models¹⁷ for each finger separately to cluster changes in the surface area (in all fingers) and TPED (only for the ring and little finger, because not enough data were available for other fingers). The number of clusters was determined by the Bayesian information criterion with the restriction that no cluster would contain fewer than 2 subjects. Such models make it possible to identify groups of patients with a similar disease course.

Thereafter, we studied whether well-known typical risk factors for DD (Table 1) had an effect on short-term change by testing a difference in these risk factors for the observed clusters. We used logistic regression for binary risk factors (sex, diabetes, epilepsy, liver disease, Peyronie disease, Ledderhose disease, knuckle pads, and population) and linear regression for continuous variables (age at baseline). The significance level for all analyses was set at $\alpha = .05$.

RESULTS

Table 1 lists population characteristics. Most participants were men, and mean age of participants was 66 years (SD, 9.8 years). Mean age of onset reported by participants was 56 years (SD, 11.5 years); 49 patients could not remember their age at the onset of DD. Participants were asked whether they were exposed to vibration. The vibration intensity was calculated as exposure in hours per week multiplied by the number of years. The median vibration intensity was 85 (interquartile range, 30–245; 95% confidence interval, 2–1,941).

Most participants were measured 3 or 4 times over 20 months. The majority of rays were affected with

TABLE 2. Median Area of DD and Median TPED per Ray for Measurements With the Most Participants

Measurement	Median Area, cm ² (IQR)*	Median TPED (IQR) [†]
1	1.2 (0.7–2.1)	20.0 (10.0–31.3)
2	1.2 (0.7–2.1)	20.0 (10.0–35.0)
3	1.3 (0.8–2.1)	16.0 (10.0–30.0)
4	1.2 (0.7–2.0)	18.0 (10.0–30.0)

IQR, interquartile range.

*Rays without DD were excluded.

[†]Rays without extension deficit were excluded.

nodules or cords, and a contracture was present in 16% of the affected rays.

Table 2 shows the median surface area and TPED per ray for measurements 1 to 4. The ranges of the surface area and TPED were broad, indicating a large variation among participants. This variation also explains why the median area and TPED remained fairly stable over time, although there was a large variance in change of surface area and extension deficit among individuals.

With generalized estimating equations, we found a significant association between surface area of DD and Tubiana stage ($P < .001$; odds ratio, 3.2; 95% confidence interval, 2.6–4.1). This means that for each square centimeter increase of surface area, the predicted odds of being in the highest category (Tubiana 4) versus the other categories increased by a factor of 3.2.

The large variance between participants complicated the analysis on minimal changes of DD. Therefore, we studied whether clusters in change profiles were present with a latent class model. We found 3 to 6 different clusters per finger on change in surface area (Fig. 2). The figure shows for each finger that not only increase but also decrease and stability of disease can occur on average in 5% to 43%, 11% to 40%, and 44% to 75%, respectively, of patients. Regarding change in TPED, fewer clusters were found. Figure 3 illustrates the course for the ring and little finger, because not enough data were available for the other fingers. In the left ring finger and the right ring and little finger, 3 clusters were formed: one cluster that increased quickly, a second cluster that remained fairly stable, and a third cluster that showed regression over time. In the left little finger, the cluster that regressed was not present.

We studied whether the disease course was influenced by one or more risk factors (Table 1), but none of these variables could explain the variance in the short-term course of the disease or the presence of different

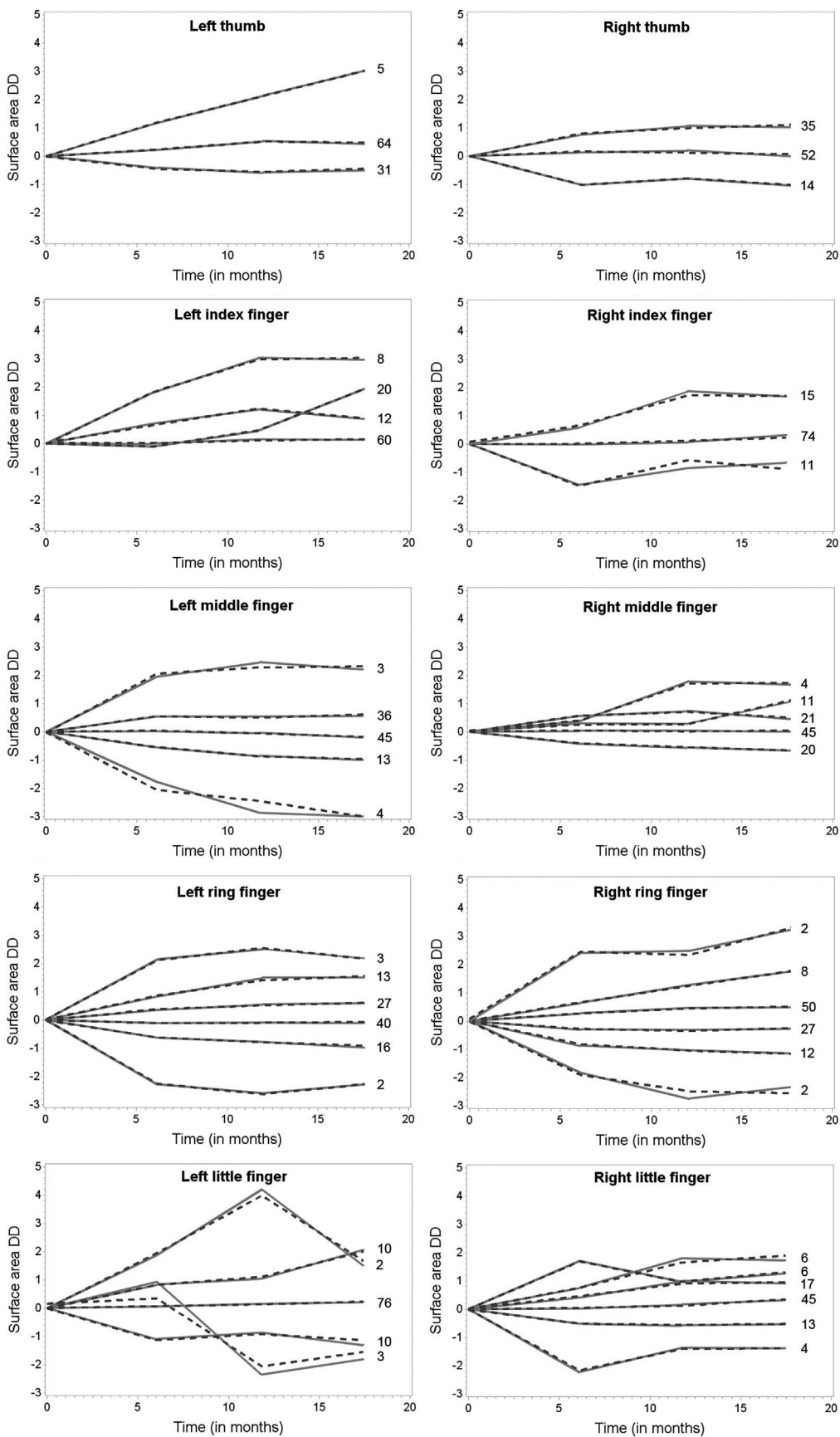


FIGURE 2: Clusters of change in surface area in square centimeters. In this analysis, the surface area was subtracted from the baseline surface area so that every participant starts at zero. The figure shows the rounded percentages of patients (on the right) in each cluster with the increase, decrease, fluctuation, and stability of disease in different fingers. Solid lines show observed values; dotted lines show predicted values.

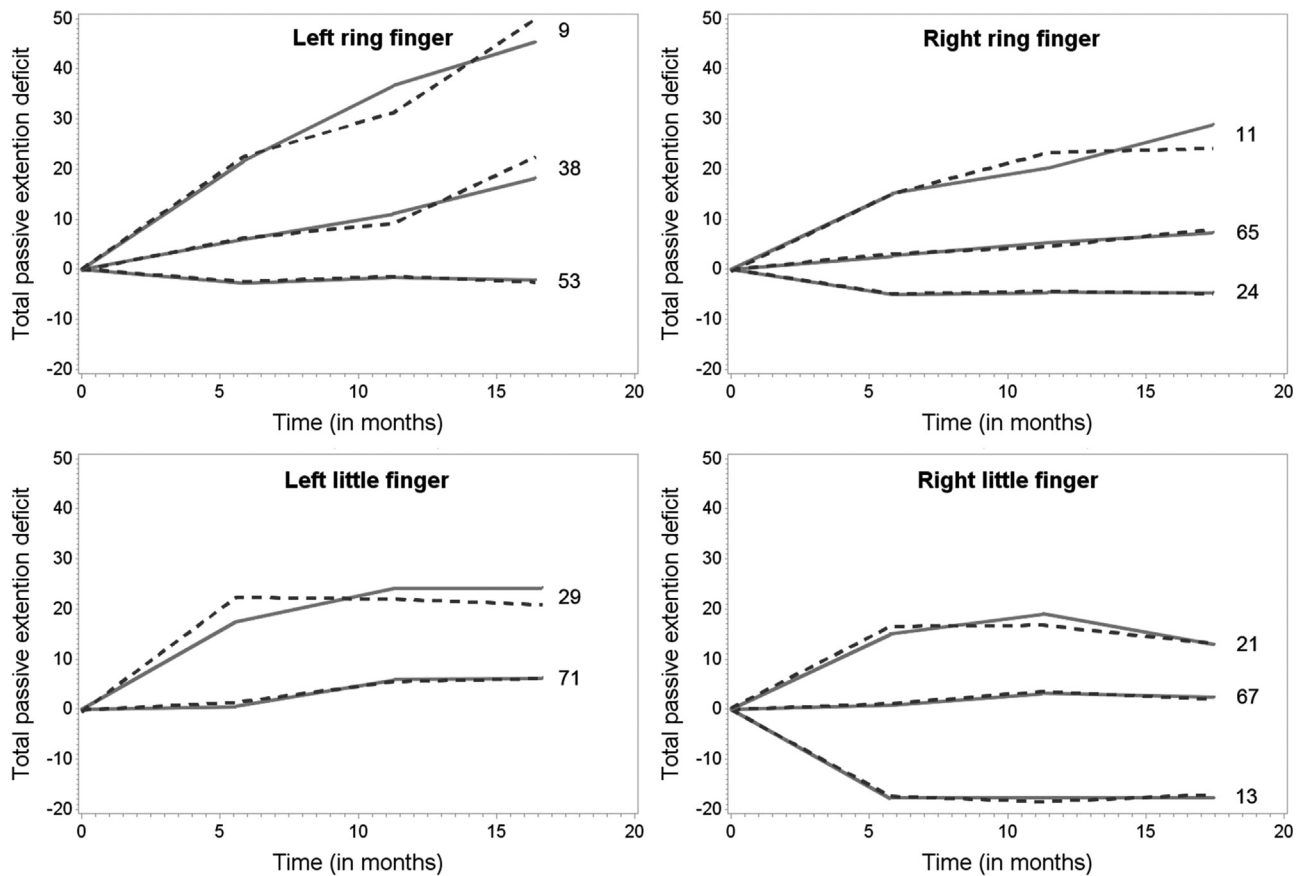


FIGURE 3: Clusters of change in TPED, in degrees. The change is shown for the ring and little fingers because not enough data were available for other fingers. The figure shows rounded percentages for patients (on the right) in each cluster with the increase, decrease, and stability of disease in different fingers. Solid lines show observed values; dotted lines show predicted values.

clusters. Only the surface area at baseline was identified as a predictor for the clusters on surface area in all fingers except the index finger. This means that participants with a smaller surface area at the start of the study were more likely to be in the regressive cluster. This association could not be proven for TPED.

DISCUSSION

The aim of this study was twofold: first, to investigate the natural course of DD systematically over short time increments, and second, to study the association between potential risk factors and this short-term disease course.

On average, the area and TPED increased only slightly in 1.5 years. However, there was a large variance in the short-term course among individual participants. Part of this variance could have been caused by measurement errors although this effect was expected to be small, because all measurements were performed by the first author, and it has been shown that intraobserver agreement on measurements of area and TPED is high.^{14,18}

Second, we identified different clusters in the short-term course of the disease based on surface area and TPED (Figs. 2, 3). All of these clusters differed significantly, which means that statistically, each line represents a different disease course. However, with respect to the disease course of the area, some of these statistically significant different clusters were closely related (ie, the course of the disease did not differ much). For example, as shown in Figure 2, in both ring fingers 3 clusters on the area are closely related and show a fairly stable disease course. Thus, it could be discussed whether these statistically significant different clusters should be seen as different clusters clinically or whether these clusters could be merged in clinical interpretation. For example, in both ring fingers, 6 statistically different disease courses can be identified but 4 different clusters exist clinically. The Bayesian information criterion indicated that there were statistical differences between clusters. We found an increase in surface area of 5% to 43%; however, a minimum increase of 2 cm² in the area of DD was seen in less than 10% of participants. In studies on the long-term course of the disease, higher percentages of progression were

seen, ranging between 34% and 51%.^{8,9,19} Notwithstanding, Reilly et al⁸ also noticed stable disease or even regression in almost 50% of patients.

Because we could identify no clear overall short-term course of the disease, it was not possible to associate risk factors with the disease course. In studies on long-term disease course, only European ethnicity and age of onset younger than 50 years were reported as predictors for disease progression.^{8,9} However, we noticed that it was challenging for participants to remember their age at onset, so the predictive power of this variable should be interpreted with caution. Regarding different clusters in disease course of surface area, only the area at the start of the study was associated with these clusters. Patients who are referred to the hospital usually have more advanced disease (ie, a higher Tubiana stage with a larger surface area of DD). Therefore, it would be expected that these patients would be more likely to be in the cluster with progressive disease. This may explain why clinicians who especially care for these patients with more advanced DD have the impression that DD is always progressive. On the contrary, participants with Tubiana stage 1 or higher did not all show progression, and a substantial proportion improved.

Our results could influence the conclusions drawn from studies in which patients with only nodules and cords were treated. For example, radiotherapy has been found to be effective in preventing disease progression of early-stage DD.^{20,21} Especially on short-term follow-up, patients who received radiotherapy showed no progression or even remission of disease. Our results show that this could be explained by the natural disease course of DD. Furthermore, long-term results after radiotherapy show progression of disease in 31% of treated hands,²¹ which is in line with the long-term progression rates of untreated patients in previous studies and with our results.^{8,9} In addition, once the natural disease progress has been elucidated, the results can be used in studies on the effect of the use of an orthosis and/or stretching on the course of the disease.

One of the strengths of this study is the large number of participants, with 370 primary affected hands. Furthermore, almost all participants originated from the northern Netherlands, which enlarged the homogeneity of the study population.¹ However, it will be interesting to see whether the course of DD in this Dutch population is comparable to the course in patients from other countries. In studies with participants only from a hospital population, usually mostly men are included in the sample.^{22–24} We included a larger number of women than in most clinical studies, and the mean age was somewhat higher.²⁵ Nonetheless, we believe that our sample gives a broad insight to the natural course of DD.

A limitation of this study is that we used nonvalidated instruments; however, we used the same instruments for all measurements. Besides, in clinical practice many different goniometers are used that are not validated. Furthermore, our data on risk factors were reported by participants. This enlarges the risk of recall bias, especially regarding the variables of age of onset, hand injury, and exposure to vibration. In addition, the prevalence of Peyronie disease might be underreported owing to the reluctance of participants to discuss this subject. To address this limitation, we interviewed all participants at every measurement and used the average of the answers in the current analyses.

This study on the natural disease course of DD showed that in the short term, the disease is stable in most participants, especially in early-phase DD, but that also progression and regression of disease occur. This knowledge contributes to the general understanding of the disease and to the evaluation of short-term results of noninvasive treatments. Furthermore, it can affect the design of new studies because it is clear that longer follow-up is needed to study the effect of treatment beyond the variance in the short-term course of the disease.

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JOURNAL CME QUESTIONS

Clusters in Short-term Disease Course in Participants With Primary Dupuytren Disease

The three stages of Dupuytren contracture progression are:

- a. Active, stable, and quiescent
- b. Proliferative, involutinal, and residual
- c. Progressive, contractile, and stable
- d. Propulsive, exudative, and contractile

Typical ectopic lesions of Dupuytren disease include which of the following:

- a. Ledderhose disease and calluses
- b. Fibroma nodules and Heberden's nodes
- c. Peyronie's and knuckle pads
- d. Notta's nodes and epidermal cysts

The behavior of Dupuytren disease is most correctly termed as:

- a. Progressive, with predictable formation of nodules and cords
- b. Variable, with some people progressing, some showing stability, and some regressing
- c. Aggressive, with fast growth requiring early surgical intervention
- d. Regressive, with most nodules or cords disappearing in 5 years

When evaluating the relationship between the surface area of Dupuytren disease and the Tubiana stage, this study showed:

- a. Greater surface area involvement correlated with advanced Tubiana stage.
- b. Lower surface area involvement correlated with advanced Tubiana stage.
- c. There was a 50% inverse relationship between surface area and stage.
- d. There was no correlation between surface area involvement and stage of disease.

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