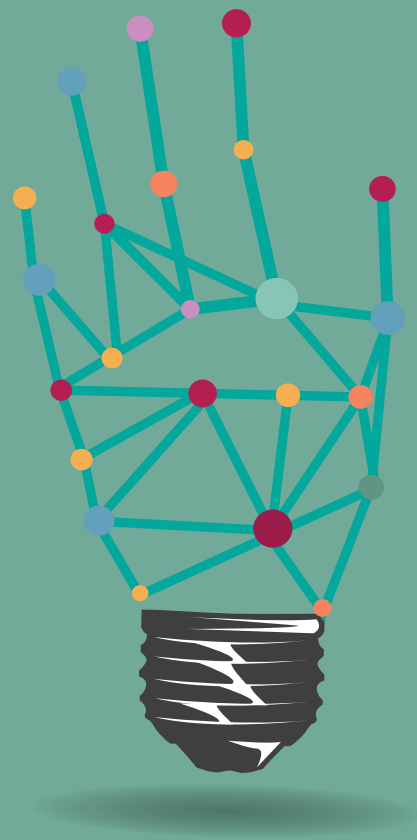

General discussion and future perspectives

Chapter 7

Dupuytren Disease is at present an incurable chronic disease that is treated symptomatically, and currently there are no possibilities to cure or prevent DD. In recent years, the focus of research was on genetics, cell and molecular biology, and treatment of DD. First, in the field of genetics, a major breakthrough was Dolmans et al.'s discovery of the genetic origin of DD.[1] Thereafter, a limited number of studies has been published on this topic and we are waiting for the succession of this research and the clinical implications.[2-5] Second, in cell and molecular biology, studies have focused on the myofibroblast, which is the cell deemed responsible for the expression of the disease. Furthermore, factors were studied that stimulated or inhibited myofibroblast contraction, such as matrix metalloproteases (MMPs).[6] Among others, it has been shown that tumor necrosis factor (TNF) promotes differentiation from fibroblasts into myofibroblasts, and that adipose-derived stem cells can inhibit proliferation of the myofibroblast.[7,8] This knowledge about TNF may offer entry points for future treatment of the disease. Currently four treatments are mostly performed in DD: dermofasciectomy, limited fasciectomy, percutaneous needle fasciotomy, and injection with collagenase *Clostridium histolyticum*.[9] They all have benefits and drawbacks that have been studied extensively.[10-16] However, the perfect treatment for DD has yet to be discovered.

Notwithstanding the efforts that are being made by all researchers in the field, there are still many aspects unknown, which, if revealed, will contribute to a better understanding of the disease. This includes prediction of the prevalence of DD, preferably based on the presence of risk factors; and second; foreseeing in which phenotype DD will occur in patients, i.e. which patterns exist in combinations of affected fingers. Third, once the disease has emerged, it would be an accomplishment to predict a patient-specific disease course over time, based on specific factors that are associated with this course. Ultimately, if the results of these and other studies can be combined, then the ability is near to define who should be treated and at what moment in time, and which treatment is the best patient-specific choice.

This thesis was designed to contribute to these aspects that previously did not receive sufficient attention and focused on gender specific and age-related prevalence rates. This thesis also introduced a new measurement method for early DD; and meticulously studied disease patterns and the short term course in DD. The findings and their implications will be outlined and put into perspective below.

Studies on the prevalence of Dupuytren Disease and risk factors in the general population

Prevalence of DD has been the subject of numerous studies in the last 50 years, however, data was lacking from the general population in The Netherlands. In Chapter 2, we studied this prevalence of DD in The Netherlands and found it to be as high as 22.1% in patients of over 50 years of age. In our random sample of the general population of Groningen, the number of patients with contractures or with recurrent disease was relatively low (18.9% and 4.1% of affected participants, respectively) when compared to the experience of surgeons active in the field, who mostly see patients with extension deficits and/or recurrent disease.[17,18] The question rises whether we have been looking at a different population than the one seen by surgeons, or that we have studied very early disease in patients from the same population.

In favor of the first theory is the study by Rayan that has suggested that two forms of DD can be distinguished: a form with a late age of onset and a mild course, not necessitating treatment, and a more aggressive form that develops at younger age and requires (repeated) treatment.[19] We calculated that the median age of our sample was 62 years, which is in line with the mean age at which most referred patients have their first treatment.[20] This indeed suggests that the aggressive form that requires treatment develops at a younger age, and that surgeons see a selected population which is not comparable to a random sample of the general population. However, the second theory is supported by the fact that a large part of the participants with DD had not noticed the disease at all by themselves, or that it was so mild that it did not worry them and therefore did not (yet) lead to a visit to the general practitioner, nor referral to a surgeon. With our prevalence study, we were unable to fully clarify whether different populations exist; however, the results from our study on disease course, which will be outlined below, did not show differences based on population.

The study on prevalence of DD was combined with investigating the role of certain risk factors, and we found a statistically significant association between DD and age, male gender, alcohol consumption of more than 15 units per week, family history of DD, and presence of Ledderhose Disease (Chapter 2). Using these risk factors, we developed a model that predicts the prevalence of DD at different ages with the presence or absence of these risk factors. This model contributes to the understanding of the occurrence of the disease, and enlarges knowledge of the

attribution of the different risk factors. It brings us a step closer to predicting the occurrence of DD.

In the graphs of the prediction model, the prevalence curves increase with age. However, in the highest age categories, there is a slight decrease in predicted prevalence. It has been stated that patients with DD, especially patients with a contracture or patients that have been operated on, live shorter than their controls, although the underlying cause has not been fully clarified, since not all studies corrected for confounders such as smoking.[21-23] Gudmundsson et al. found that patients with DD contractures had a significantly increased total mortality compared to participants without DD, and a higher cancer mortality (but not significant), when corrected for age and smoking habits.[22] Nine different genetic loci—that include genes involved in the Wnt-signaling pathway—play a role in the development of DD.[1] Changes in this Wnt-singnaling pathway influence cell proliferation and survival.[24] Other diseases that have been linked to abnormalities in the Wnt-signaling pathway include leukemia[25,26], a high bone mass (sclerosteosis)[27], pulmonary fibrosis[28], hair follicle tumors[27], and colon cancer[27,29,30]. It has yet to be proven that these diseases are linked to DD, and that the presence of such co-morbidities causes an increased mortality rate in patients with DD.

The prevalence of DD in The Netherlands is somewhere in the middle of the current reported prevalence rates of 0.2-56%, as published by Hindocha et al.[31] Since this range of reported prevalences is very broad, we decided to perform a systematic review and meta-analysis on the prevalence of DD in Western countries, and we were able to reduce the range to 0.6-31.6%. This range still is broader than we had expected. Systematic reviews and meta-analyses on the prevalence of other diseases also reported broad ranges. This was often caused by differences in the included studies regarding study design, population, diagnostic criteria, and geographic differences.[32-34] Although our inclusion and exclusion criteria were strict, we could not completely rule out heterogeneity in study design, population and geographic location as well. With respect to the latter, it has been suggested that DD is more common in the Northern countries because of hand exposure to low outside temperatures, which leads to vasoconstriction in the hands. This may result in local ischemia, which—after reoxygenation—may cause the formation of oxygen free radicals that have been found to play a role in the development of DD.[35] We question this theory because hypothermia is a very effective way to preserve natural scavenging systems in tissues, and thus prevents the deleterious effects of ischemia and subsequent reperfusion.[36-38] To elucidate the role of geographic location, we studied the association between mean outside temperature in several countries and prevalence of DD. To this end, we added geographic location to the generalized linear mixed model from our meta-analysis (Chapter 3). We plotted the random differences between the geographic locations to study an order in these locations; however, this did not demonstrate a clear trend. Figure 1 shows, regarding studies from England, that for males the prevalence found by both Bennett[39] and Burke[40] was lower than the median prevalence from the meta-analysis, while the prevalence from Arafa[41] was higher than the median, although the geographic locations are not that different. This inconsistency shows that it is difficult to draw conclusions about the relation between prevalence of DD and geographic location.

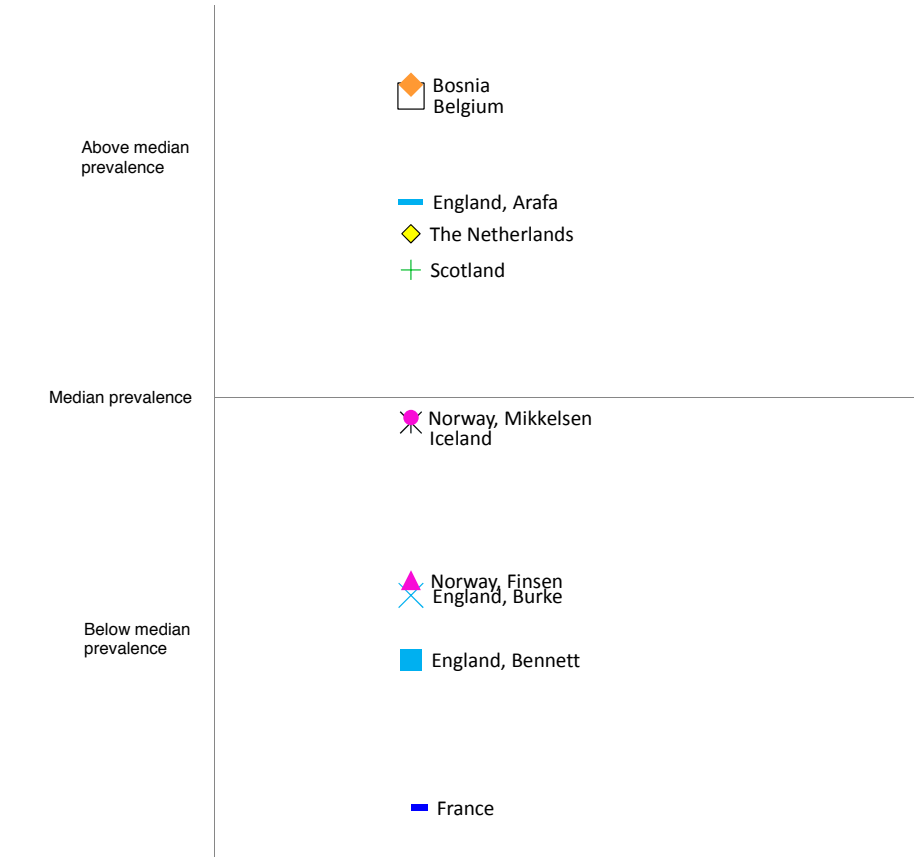

Figure 1. Relative distance of prevalence in different geographical locations to the median prevalence of males in the meta-analysis from Chapter 3. The greater the distance to the baseline, the further the prevalence deviates from the median prevalence.

The difficulties that we experienced in explaining the association between prevalence and geographic location could imply that either our approach was not correct, or that the data were not suitable to be analyzed. Comparatively, in other diseases such as multiple sclerosis and IgA nephropathy, the differences in prevalence distribution are based on genetic variation, differences in environment, and their interaction.[42,43] In multiple sclerosis, demographic epidemiology has changed in the past decades; prevalence has increased due to longer survival, and more women are affected, probably through a change in female lifestyle.[42] In IgA nephropathy, variation at genetic susceptibility loci is correlated to differences in disease prevalence among populations, and nearly 5% of the variation in disease risk could be explained by this genetic susceptibility.[43] As stated before, it has recently become apparent that nine genetic loci are associated with DD[1], and that some patients carry more risk alleles than others.[44] In line with multiple sclerosis and IgA nephropathy, it is possible that differences in demographic epidemiology and genetic susceptibility also account for a part of the differences in prevalence rates of DD.

Measurements of disease severity in Dupuytren Disease

In order to study disease patterns and the natural disease course of DD accurately, it was essential to use a classification that covers all stadia of DD in a suitable manner. Different classifications exist to categorize the severity of DD. Most of these classifications focus on extension deficit of the fingers[46-49], and patients with a contracture of the fingers are divided into three or four categories, while patients without an extension deficit are all merged into one category. However, as shown in previous studies[50,51] and confirmed by the results of Chapter 2, the general population has a low rate of patients with contractures, which makes these classifications less suitable for studies in this population without contractures.

For patients with only palmar disease, no standard measurement method existed to indicate disease severity. In previous studies, marking nodules and cords was used to assess the effect of radiotherapy in patients with early DD.[52,53] However, it is unclear how the exact treatment effect was measured since only "regression", "progression", or "status idem" were determined[54], without reporting whether measurement of the actual size of nodules and cords was performed.[53,55] This makes it difficult to interpret the exact effect of radiotherapy in early DD.

In Chapter 4, we have introduced the measurement of surface area as a new parameter of disease expression in patients without an extension deficit. Both intra- and inter-observer agreement of this measurement was high, and in Chapter 5 we have shown that there is a strong association between surface area and Tubiana stage. It should be noted that in patients with advanced disease, drawing and measuring the surface area becomes rather cumbersome and time-consuming. However, we showed that even someone without experience in diagnosing DD is able to accurately diagnose and measure DD after a relatively short training. Therefore, we believe that this new measurement is very useful to quantify change of disease in patients without an extension deficit, both in scientific research as well as clinically since it helps a surgeon to objectively determine disease progression.

In patients who, in addition to palmar disease, experience a contracture of one or more fingers, goniometry is used to measure the severity of the disease. The severity of a contracture is commonly used as an outcome measurement for recurrence after treatment, although, no clear definition of recurrence currently exists.[56] Furthermore, the measurement of contractures has been reported in numerous different ways, including "total flexion deformity"[53], "degrees of flexion"[57], "degree of extension lag"[58], "active extension loss"[59], "total extension deficit"[60], and "total passive extension deficit"[20]. This variety in reporting measurements of a contracture complicates comparison of the results, and moreover, the reliability of these measurements has not been studied thoroughly.

Therefore, in addition to agreement on measuring surface area, we studied the agreement in the determination of total *passive* extension deficit (TPED). This was the first study that investigated both intra- and inter-observer agreement of TPED in patients with DD. Previously, only one related study was performed regarding the reliability of measuring the *active* extension deficit. However, this study comprised a very small sample of 13 patients with DD, and only interrater reliability was investigated, which was found to be 0.949 for total active extension.[61] Our results, derived in a large sample of 54 patients, show that also *passive* measurement of the extension deficit has a high intra- and inter-observer agreement. Although the total active extension deficit (TAED) might correspond better with the patient reported disability, it is conceivable that the result of this measurement is dependent on the ability of the patient to powerfully extend the fingers, as well as on the evaluation of the investigator. When measuring passive extension deficit, the result is only dependent on the measurement of the investigator. Therefore, in our opinion, it is favorable to study passive extension deficit in patients with DD.

Disease patterns in Dupuytren Disease

Prior to studying the disease course of DD, we felt the need to study disease patterns in primary disease thoroughly. In other conditions, disease patterns are of interest to predict outcome or disease course as well. For example, in dermatology it is used to study development of naevi[62], in pulmonology to study the development of chronic thrombo-embolic pulmonary hypertension after pulmonary thrombo-embolism,[63] and in neurology, patterns of brain atrophy are used as marker for cognitive decline in patients with Parkinson's disease[64].

Regarding disease patterns in DD, several empirical articles—without firm statistical analyses—have been published. From these articles it has been deduced that the ring finger and little finger are correlated in DD, and that an affected radial side is accompanied by more severe disease in the ulnar side of the hand.[46,65-67] In Chapter 5, we studied in detail the presence of disease patterns, and tested these assumptions. In our cohort, most often one or two fingers were affected, and DD in all five fingers simultaneously was rare. Taking into account age and gender, the following fingers were correlated regarding disease severity: thumb and index finger; middle finger and ring finger; and middle finger and little finger. No relation could be proven between severity of DD and age and gender, although our results suggest that males and older patients have more severe disease. It has been reported that younger patients experience a more aggressive form of the disease and an earlier recurrence after treatment.[13] Our results lend support to the theory that patients with an aggressive form will have a more severe disease already at younger ages, since thereby the overall effect of age on severity will be reduced. The supposed correlation between the ring finger and little finger, and between the radial and ulnar side could not be confirmed, which is a new and valuable finding. It means that disease in the ulnar side is not a predictor for occurrence of DD in the radial side of the hand.

Our findings are important in the context of treatment and prevention. Since it is now clear that some fingers are correlated with respect to disease occurrence and severity, it may be wise to treat these fingers simultaneously. On the contrary, since there is no correlation between the ring finger and the little finger, our results suggest that it is justifiable to solely treat a contracture of the ring finger, even when a nodule or cord in the palm of the little finger is present as well.

Short term disease course in primary Dupuytren Disease

Dupuytren disease is known as a chronic disease, and is thought to be progressive over time, at least in many cases. However, until now, the disease course has been studied with one moment of follow up only,[57,59] and consequently, the exact course over time is not known. It is important to study disease course in DD, since the indication for (surgical) treatment is a MCP joint contracture of >30 degrees or a PIP joint contracture of >20 degrees with *documented progression*.[68]

We prospectively investigated the disease course with predefined intervals of six months in participants with primary disease (Chapter 6). For investigation of disease course in cases with only nodules and cords, but no contractures, we used our new measurement of surface area. To determine disease course of contractures, we analyzed changes in TPED.

The most important finding was that progression and regression of the disease occurs, but that overall, the disease is stable in the majority of patients during one and a half years of follow up. Furthermore, we showed that the variation in short term disease between cases was large (without being caused by measurement errors). These findings have very important clinical implications. Firstly, the findings could affect the conclusions derived from studies in which patients with early stage disease were treated for DD. For example, radiotherapy has been found to be an effective treatment for nodules in the proliferative stage.[54,55] On the short run, patients who received radiotherapy showed no progression or even remission of disease. Our results show that this could also be explained by the natural disease course of DD, and therefore, the results of these studies without a control group should be interpreted with caution. Secondly, our results can be very useful in the design of new studies since it is now clear that a prolonged follow-up is needed to study the effect of treatment beyond the variance in short term disease course, especially if it concerns the effect of treatment in patients with early-phase DD. Thirdly, it is disadvantageous to intervene too early, since there is a high rate of recurrence after treatment.[13] Knowledge of the natural disease course is of interest in relation to the moment of treatment because in case the disease is stable or even regresses after a while, treatment may not be necessary.

We studied whether certain risk factors could be linked to the differences in short term disease course. Only the size of the surface area at the start of the study could be linked to the different clusters in course of the surface area. No other associations were identified, which could be caused by the large variation in

disease course between cases. Besides, the study population has been subjected to selection bias, since patients with extensive disease or an aggressive disease course were operated on, and therefore dropped out of the study. As a consequence, particularly participants with mild DD will remain in the study, and the curve of progression will flatten. This makes it more difficult to find an association between disease course and risk factors. A third consideration might be that risk factors only play a role in the onset of both primary as well as recurrent disease, and that once the disease is present, disease patterns and disease course are no longer influenced by these external risk factors. Perhaps that increased knowledge about genetic risk profiles can provide clarity on this topic.

Strengths and limitations of this thesis

One of the strengths of this thesis is the cross-sectional and prospective design of our studies in which all participants were physically examined. This physical examination enlarges the reliability of our outcomes, especially compared to studies that collected data with questionnaires only.[69,70] Furthermore, our study samples are large in comparison to other studies regarding prevalence[71,72], agreement on measurements[61,73], and disease course[57,59,74]. Another strength is the use of extensive statistical analyses, in which particular attention was paid to the fact that most of our data is correlated. To our knowledge such analyses are not frequently used in studies on DD.

Several limitations of our research should be noted. In this thesis, the study populations of Chapter 2, 4, 5 and 6 are closely related. In our design and analyses, we have tried to control for bias and confounders. However, if any undetected selection bias was present in our population, this will have influenced several studies in this thesis. Furthermore, this study population originated from the northern Netherlands, and therefore it might not be possible to extrapolate our results directly to other parts of the world. Notwithstanding this specific population, our results regarding prevalence of DD and occurrence of DD among fingers are comparable to previous publications from Europe[50,65,66,72] and Japan[67].

In this thesis we focused on patients with primary DD, which causes selection bias, especially in relation to severity of disease. Most of our participants were affected with nodules and cords, but without contractures of the fingers. Therefore, our results might be less applicable to tertiary hospitals that mainly treat patients with severe primary disease or with recurrent disease after previous treatment.

Future perspectives

In Chapter 2 we studied the association between prevalence of DD and risk factors; however, it remains a challenge to pinpoint at associations within diseases that probably have a multifactorial origin. Furthermore, in a cross-sectional study it is not possible to determine a causal relationship, and therefore, a prospective cohort study would be a more suitable design for such research question. In the northern Netherlands, a large observational follow-up study called LifeLines is currently running, with 165,000 participants covering three generations.[75] If studying the occurrence of DD could be included in the measurements of LifeLines, the causal relationship between DD and previously supposed risk factors could be clarified. Preferably, this should be preceded by a systematic review of the literature and meta-analysis on this topic, to get an overview of the risk factors that should be taken into account, and to which extent these factors are expected to contribute to the onset of DD.

Based on the results of Chapter 4, we concluded that preferably the TPED should be used in patients with DD, instead of TAED. However, to substantiate this statement, and to make it possible to compare results of studies that use either TPED or TAED, it would be interesting to study the agreement between the active and passive measurement. For example, the TAED could be measured in patients who were all found to have the similar TPED. If active measurement is reliable, than the outcome of measuring the TAED should be comparable in all of these patients.

In Chapter 5, we studied the correlation between fingers on occurrence and severity of DD, and in this general discussion the potential implications for surgical treatment were discussed. However, before definite conclusions on this topic can be drawn, the correlation between fingers on progression of disease should be studied as well.

In chapter 6, the results on short term disease course were presented. For future research, this cohort should be followed for several years to investigate the long term disease course. In addition, the patient reported disability should be studied more extensively, which is especially important in our aging population with prolonged working life. Furthermore, in studies that focus on treatment outcome, occurrence of recurrence is often studied as an outcome parameter. It will be complementary to enhance our knowledge about the course of recurrent disease after different treatment modalities. Such study could facilitate the decision making process to choose the most favorable patient-specific treatment.

It has been shown that DD is a complex disease, and genetic factors play an important role in disease susceptibility.[1] These factors, for example genetic risk score based on the number of affected SNPs, should be taken into account in the previously mentioned future perspectives.

Conclusion

The studies in this thesis have contributed our knowledge about prevalence, measurements, disease patterns, and short term disease course of DD. If our results will be combined with the results of previous and future studies, we are closer to predicting the right treatment at the best time for each patient individually, and this is a step towards a cure for DD.

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