Epidemiology of Dupuytren disease unraveled

Broekstra, Dieuwke

GENERAL DISCUSSION

This thesis provides more insight into prevalence, risk factors, measurement uncertainty and disease course of Dupuytren disease. In the current chapter, the primary findings are discussed and placed in a wider context. Furthermore, implications for future studies and clinical practice are presented.

Prevalence

The previously reported prevalence range in the literature was 0.6 – 56.0%.[1] In a meta-analysis, we were able to reduce this wide range to 0.6 – 30.6%, by focusing on general populations and studies of high quality (Chapter 2). Additionally, prediction limits were presented as function of age for men and women separately, so that the results of this study can be used in different Dupuytren populations elsewhere. Especially for younger ages, the results of our study can be useful for estimating the prevalence, as there is little known about prevalence rates at younger ages. In Appendix 8.1, the estimated prevalence rates as reported in Figure 2 of Chapter 2 are presented in a table.

The in Chapter 2 reported prevalence range is still wide. This is probably caused by differences in definition of diagnosis, or by differences in populations. We aimed to provide prevalence ranges of populations worldwide, but we mainly found studies that originated from Europe, and a few that originated from the Far East. Therefore, the reported prevalence range holds true for Western countries. However, the prediction limits take heterogeneity between studies into account, and therefore, the results of the meta-analysis may be extrapolated to other parts of the world as well, if heterogeneity in our study is representative for other continents.

Nowadays, there are increasing numbers of publications reporting the presence of Dupuytren disease on other continents, like Asia,[2,3] as well as an increasing number of case reports of Dupuytren disease in Asia and Africa.[4-6] A recent study even reported 75 Dupuytren cases in Ethiopia.[7] Although this raises doubt on the hypothesis that Dupuytren disease originates solely from the Celts or Vikings as genetic mutation and was spread by migration,[8] it is important to realize that this finding provides no information on prevalence.[9] Even though it is known that Dupuytren is heritable,[10-13] heritability does not explain all the present cases of Dupuytren disease.[14] There

are other theories on why the disease appears to be more prevalent in Northern countries. For instance, it is likely that Dupuytren disease is underreported on other continents, since Europe has more centres involved in Dupuytren disease research. Furthermore, certain risk factors might play an important role in the development of the disease,[4,14] as will be explained in the following section.

Risk factors

In Chapter 3, we investigated the strength and consistency of the associations between Dupuytren disease and diabetes mellitus, liver disease and epilepsy. We found an association between Dupuytren disease and diabetes mellitus, adjusted for age. Although we cannot prove that Dupuytren disease develops as consequence of diabetes mellitus, the results of this study support the hypothesis that advanced-glycated end-products (AGEs), which are produced as result from non-enzymatic glycation of proteins as consequence of diabetes mellitus,[15,16] cause upregulation of transforming growth factor-β (TGF-β).[17] TGF-β is known to be upregulated in Dupuytren tissue, and leads to synthesis of collagen.[18-21] Moreover, collagen cross-linking increases as consequence of non-enzymatic glycation.[22] So, it seems that cell biologic changes that occur as consequence of diabetes mellitus, might trigger the onset of Dupuytren disease. This is supported by the finding that the association between Dupuytren disease and diabetes mellitus type 1 was estimated stronger than for type 2, although this difference was not statistically significant.

Further, we demonstrated an association between Dupuytren disease and liver disease (Chapter 3), although we could not adjust the analysis for alcohol consumption due to lack of reporting. In addition to various studies reporting an association between Dupuytren disease and liver disease, there are also several studies that report an association between Dupuytren disease and excessive alcohol consumption.[23-26] Especially the study of Lanting et al., in which an age-stratified random sample of the general population was included and physically examined for presence of Dupuytren disease, demonstrated a strong association between excessive alcohol use and the presence of Dupuytren disease.[24] Although it might be that not alcohol consumption itself, but rather liver dysfunction that occurs as a consequence of prolonged alcohol abuse triggers the onset of Dupuytren disease, the scientific support for this hypothesis is very limited,[27] and no explanations for

the disease mechanism were found. In two studies, subgroups (alcoholics with and without liver disease, patients with alcoholic and non-alcoholic liver disease) were compared for the presence of Dupuytren disease.[27,28] Unfortunately, the two studies reported contradictory findings with respect to the role of alcohol consumption in the association between Dupuytren disease and liver disease. Furthermore, it has been suggested that smoking explains part of the association between Dupuytren disease and alcohol use.[29] However, recent large studies have not identified smoking as risk factor for Dupuytren disease.[23,24,30] So, it remains unclear what the role of alcohol consumption is in the association between Dupuytren disease and liver disease.

We also demonstrated an association between Dupuytren disease and epilepsy. It is thought that the use of anticonvulsant drugs (barbiturates) plays a role in this association, but we could not adjust the analysis for this. Alterations in liver function as consequence of the use of barbiturates has been suggested as causal pathway,[31] but others suggested that barbiturates might have a direct effect on soft tissues.[32] The observation that the number of papers on this topic decreased over time, indicates that the focus in Dupuytren research has shifted to other areas of interest. The literature review and meta-analysis was aimed to end speculations on the association between the two diseases, taking the role of anticonvulsants into account. Although we could confirm the presence of an association, we could not investigate whether specific drugs were responsible for this association.

In Chapter 4, we reported a strong association between field hockey playing and the presence of Dupuytren disease. It is known that mechanical stress is crucial for the formation of myofibroblasts.[33] So, it is likely that forces applied to the hand during field hockey playing trigger Dupuytren disease at the long term. However, neither a dose-response relation was found, nor an association between dose and Dupuytren disease severity. A sensitivity analysis did not yield a different result. The question may be raised why we did not find a dose-response relation. It is important to note that there are many biomechanical aspects of field hockey playing that are unknown. For instance, the hand consists of many different segments that are connected to each other with joints. It is unknown what the influence is of a field hockey shot on all these different segments. Furthermore, we do not know how the forces resulting from a shot are transferred from the stick to the hands. Next

to that, the material of which the field hockey stick is manufactured is expected to play an important role in the mechanic properties of the stick, as this has been demonstrated in baseball bats and ice hockey sticks.[34,35] Moreover, it is possible that not the size of the force vector applied to the hand, but rather the volume of force (combination of size and duration) determines the exposure. In addition to this, the recovery time between subsequent exposures might be relevant as well. Another explanation for the absent dose-response relation might be that field hockey playing alters the extra-cellular matrix stiffness through mechanoregulation,[36] starting a cascade that eventually leads to extra-cellular matrix remodeling, increased tissue stiffness and subsequent myofibroblast contraction. This cascade can be considered as a feed-forward loop, that once it has been triggered, it is self-perpetuating.[37,38] With this in mind, the absence of a dose-response relation might be less surprising. Furthermore, this mechanism is supported by the findings in Chapter 7, that indicate that there are also patients who show disease regression over time. A dose-response relation would be easier to identify when all participants experience progression. Since this is not the case, a dose-response relation in Chapter 4 might be masked by those experiencing regression.

Measurement instruments and outcome parameters

As in our cohort study (Chapter 7) two observers were involved in the measurements, we quantified the inter-observer variation in order to determine whether adjustment for observer was necessary. So, we determined the intra- and inter-observer agreement on frequently used outcome parameters in Dupuytren research (Chapter 5). We also introduced a new outcome parameter for Dupuytren research: area of nodules and cords. This new parameter was introduced since the majority of the participants in the cohort study on natural disease course (Chapter 7), did not have contractures. In such cases, disease extent cannot be determined by measuring extension deficit in a finger. Determining change over time or change after treatment can be challenging when no suitable outcome parameter is available. In previous studies, classifications were used to indicate change,[39-41] or other qualitative measures such as 'mass reduction yes/no' were used to indicate regression.[42] However, it is clear that such outcomes are less sensitive, and some might suffer from subjectivity. The parameter area of nodules and cords forms an

objective outcome parameter that is suitable to detect subtle changes in disease course (maximal standard error of measurement (SEM) was 0.4 cm^2, both for intra- and inter-observer measurements), and that is easily measured.

For more severe cases of Dupuytren disease, characterized by the presence of contractures, range of motion is most commonly used to quantify severity.[43] However, it can be measured and presented in several different ways, as demonstrated by the fact that over 17 different definitions of range of motion measurements are present in the literature. Passive extension deficit is most frequently used, and therefore, we determined the agreement on this outcome parameter as well.[43] Although the measurements of total passive extension deficit (TPED) showed high agreement most of the times, there were a few large deviations in agreement (both inter- and intra-observer), and the maximal SEM was 15°. This is in contrast to the results of a previous agreement study, reporting a maximal SEM of 3°.[44] An explanation for this discrepancy is that we assessed agreement on passive extension deficit, while Engstrand et al. assessed active extension deficit. So, active extension deficit seems to provide more reliable results. However, passive extension deficit might be preferred, since it captures the true goniometric extension deficit, and is not dependent on muscular extension lag. Furthermore, measurements of passive extension deficit are not influenced by Boutonnière deformities that are sometimes present in Dupuytren disease.[45] On the other hand, active extension deficit might correspond more closely to what the patient experiences. As long as there are no studies published in which the measurements of passive and active extension deficit are compared, it might be useful to measure and report both active and passive extension deficit to enhance comparability.

In Chapter 6, we addressed the ability of the Unité Rhumatologique des Affections de la Main (URAM) and the Michigan Hand Questionnaire (MHQ) to measure Dupuytren disease progression. Both patient reported outcome measures (PROMs) were able to detect disease progression, but only at a group level. This means that a difference in hand function between Dupuytren patients with progression and those without, can be demonstrated using the URAM or MHQ. However, individual cases of progression cannot be identified by using one of these PROMs, unless changes in hand function are large. Although the URAM was easily accepted by the participants (in contrast to the MHQ), the major weakness of the URAM can be found in the developmental stage. In this stage, only 9 Dupuytren

patients and 7 experts from the same clinic were interviewed to generate items, and their characteristics were not reported. A total of 68 items were generated, that were reduced to 9 items using exploratory factor analysis. By limiting the item generation to a few patients and clinicians from the same clinic, it can be questioned whether this sample is representative. This might be responsible for the critical note on cultural generalizability, published recently.[46] However, the URAM is the first PROM especially designed for Dupuytren disease patients, and has good clinimetric properties. Especially the question "Can you lean on your hand?" appeared to be a first indication for extension deficit. It is a short PROM, and is less sensitive to progression than the MHQ, but it can easily be implemented in clinical practice owing to the small number of items. However, it might be worth to make an inventory of the activities that are most frequently reported by Dupuytren disease patients when asked about what they experience as the most disabling. Adaptation of the URAM or development of a new PROM for Dupuytren disease might be useful, taking the trade-off between (cultural) generalizability, sensitivity and questionnaire length into account.

There are many different PROMs available that are designed to measure hand function. In Dupuytren research, the Disabilities of Should Arm and Hand questionnaire (DASH) is used most frequently.[43] Lately, new Dupuytren disease-specific PROMs have been developed, such as the Southampton Dupuytren Scoring Scheme (SDSS)[47] and the URAM.[48] It seems that the search for a suitable PROM for use in Dupuytren disease patients, continues. However, it is important to note that there is no, and there will not be a single ideal PROM for use in Dupuytren research. Which instrument should be used depends largely on the research question and consequently, the outcome measure of interest. For example, a ruler might seem suitable to measure the length of an object. However, this only holds true when the object's dimensions are within a certain range. This is exactly what was emphasized in Chapter 6; the fact that both PROMs are able to detect change after treatment, does not necessarily mean that they are able to detect disease progression. Related to this, the fact that a PROM "has been validated" (as often stated in the literature), does not mean that this PROM is suitable for use in each population or in each individual. The clinimetric properties of the PROM are depending on the population in which it is used.

Disease course

The primary finding in Chapter 7 is that on average, Dupuytren disease tends to progress over time for both outcomes area of nodules and cords, and TPED. However, there were also cases with disease regression. Further, the speed of progression varies between participants with and without Ledderhose disease, and between participants from the general and hospital population. In the interim-analysis of this study, no risk factors were associated with progression.[49] It is possible that the elapsed time (1.5 years) was too short for progression to occur in the majority of the participants, which is supported by the finding that only a small amount of participants showed progression.[49]

From our results, it is clear that the hospital and general population are not the same. The question what exactly defines these populations, is difficult to answer. Although a distinction within the Dupuytren disease population (Dupuytren disease and non-Dupuytren disease) has already been suggested in the literature,[50] the reported characteristics for the non-Dupuytren disease cases are not fully in line with the characteristics in our general population (see Appendix 7.2). Furthermore, the majority of the covariates on which participants of the general and hospital population differed in our cohort, were not associated with progression. This suggests that an explanation for the distinction between these populations should not be sought in clinical characteristics, but rather in other factors.

A limitation of the measurements of area (Chapter 7), is that area is only measured in two dimensions. We assumed that growth of Dupuytren tissue occurs with a similar speed in all three dimensions, but it is unclear whether this assumption is justified. It might be interesting to evaluate this assumption, for instance by using ultrasound (although ultrasound also provides 2D images, but in different planes than area) or magnetic resonance imaging (MRI).

Many participants included in the cohort study in natural disease course were treated during the study. Although the data from their treated hand was not used in the analyses of Chapter 7, measurements of the treated hand were continued (or in participants with bilateral treatment, they were invited to continue participation). So, we have data to describe the disease course of recurrent Dupuytren disease as well, but we will investigate this in more detail in a future study. We further noticed that some participants were treated once, and showed full recovery without

any recurrences (not even fibrous masses in the treated area). Others were treated multiple times on the same ray during the course of the study, and suffered from multiple recurrences. It appears that the Dupuytren disease population can be divided in subpopulations: those with an aggressive form of the disease, and those with a mild form. This has previously been recognized in other studies.[51,52] Future studies should focus on the former patient group, as prevention of recurrence would reduce the burden of this disease largely. Further, efforts should be made to develop a model that enables us to predict the course of Dupuytren disease. There are many cohort studies reported in the literature that examine the course of certain diseases,[53-56] but prospective cohort studies following the participants on a regular basis are less common. An example of a cohort study with regular follow-up is the Lifelines cohort, including over 167,000 participants from three generations in the Northern part of the Netherlands. Since Lifelines contains information on various aspects that we did not collected in our cohort study, such as laboratory assessments, it might form a valuable source of data to study some of the questions that remain unanswered in this thesis.

Advantages and limitations of mixed effects models

As explained in Chapter 1, many datasets in Dupuytren research are characterized by a multilevel structure. Datasets with this structure can be analyzed using mixed-effects models. As multiple chapters of this thesis are statistically supported by mixed-effects models, some of the advantages and limitations of these analyses are pointed out here.

The main advantage of mixed-effects models is the absence of the assumption that the observations are independent, which has already been discussed in Chapter 1. Another advantage is that the number of observations does not have to be the same for each participant. Furthermore, time can be included as continuous parameter, so that it is not necessary that participants are measured at equal time intervals. This is in contrast to the analysis of variance (ANOVA). Especially in cohort studies as described in Chapter 7, it is impossible to measure each participant on each moment and on exactly the same time intervals. So, mixed-effects models are very flexible and can be applied to a wide variety of outcome parameters.

The flexibility of mixed-effects models also forms the major disadvantage, as they are complex. Although it is not difficult to get these models 'up and running', they are versatile and have many settings that need to be set correctly. Otherwise, the model will run, but provides invalid results. Help of an experienced researcher or statistician is often necessary, but cannot always be provided. This is probably the reason why the number of publications in Dupuytren research that made use of mixed-effects models, is low.[57-59] As a consequence, it is difficult for peer-reviewers to criticize or judge the statistical methodology used in studies on Dupuytren disease.

It can be argued that the researchers using mixed-effects models should make more effort in explaining the principles behind these models, for example by providing additional information on the statistical analyses in supplemental material. This should be encouraged by journals, as it would enhance comprehensibility, transparency and the transfer of knowledge.

Implications for future research and clinical care of Dupuytren disease

The results of Chapter 2 show that Dupuytren disease becomes more prevalent with increasing age. The prevalence rates and prediction limits can be used in future studies elsewhere to estimate the prevalence rate. For example, the prevalence rates can be used in sample size calculations for future studies.

The strong association that was found between diabetes mellitus and Dupuytren disease (Chapter 3), gives a glimpse into the etiology of Dupuytren disease, and it would be interesting to investigate this association further. Especially the role of advanced-glycated end-products (AGEs) in fibroblast proliferation and collagen cross-linking should be elucidated, as non-enzymatic glycation is associated with other fibrotic diseases, such as cardiovascular, renal or peritoneal fibrosis.[60-63] As accumulation of AGEs can easily be measured in the skin using an AGE Reader,[64] it might be interesting to explore whether high AGE accumulation is associated with Dupuytren disease. Clinicians and researchers should be aware that diabetes mellitus might be a risk factor for Dupuytren disease, but whether liver disease and epilepsy should be considered as risk factor remains unclear. We also found a strong association between field hockey playing and Dupuytren disease, as reported in Chapter 4. Although causality cannot be proven, the results add to the existing knowledge that Dupuytren disease might be triggered by heavy manual activities.

Future biomechanical studies in healthy volunteers should be designed to provide normative values of the size of force applied to the hand during various activities. As there is no such information available, it is difficult to compare the load of different activities. For example, it is unlikely that the hands of a field hockey player experience the same load as the hands of a road worker involved in drilling. When such information is known, it might be interesting to evaluate the prevalence of Dupuytren disease in different occupational groups, with respect to the size of forces applied to the hand. Furthermore, the point of action of the force vectors should be studied in relation to the localization of Dupuytren tissue. This can provide insight in the role of heavy manual work and vibration to the development of Dupuytren disease, and eventually contribute to the prevention of Dupuytren disease occurring.

Chapter 5 provides results on agreement on commonly used outcomes in Dupuytren research. Although the agreement was high overall, in some cases the observer variability was high. Furthermore, the new parameter area (introduced in Chapter 5) suited the purpose of our cohort study on disease course well, but it resulted in a total area per ray, just like measurements of TPED. So, multiple observations per patient are gathered, that are clustered in a multilevel structure. This leads to several challenges in analyzing the data, as explained in Chapter 1. It might be worth to search for a new outcome measure for Dupuytren disease, that is less prone to observer variation, and yields less difficulties in analyzing the data. Such a new outcome measure should contain no more than one value per hand or per patient, to limit the number of levels in the multilevel structure. For disease extent and severity, 3D photography might be an interesting field to explore. It has very recently been used in aesthetic surgery to quantify graft loss after facial lipofilling (J.C.N. Willemsen 2017, personal communication, on March 22nd), or to quantify volume of facial compartiments or mammae.[65,66] Other applications include measuring the volume of haemangioma or the area of burn wounds.[67-69] In Dupuytren research, it might be used to quantify disease extent per hand, resulting in a total area of Dupuytren tissue. Additionally, ultrasound and MRI might form an alternative measure for quantifying disease extent. An additional advantage of MRI is that it provides 3D images of the Dupuytren tissue, while the measurement of area in Chapter 7 are based on 2 dimensions. Furthermore, few

small studies suggest that active nodules can be distinguished from inactive nodules using ultrasound, based on echogenicity of the nodule.[70,71] Future studies including a large sample that is prospectively followed over time, should be done to determine whether ultrasound is able to identify Dupuytren disease activity. If this is possible, ultrasound provides a more feasible and cheap method to quantify disease extent and determine disease activity, compared to MRI.

The ability to detect change due to progression of two PROMs, was assessed in Chapter 6. Both the URAM and MHQ were able to detect change due to progression on a group level, but both had disadvantages (scale boundary effects, length of PROM). It can be useful to establish the cultural generalizability of the URAM in different countries, as done previously in the United Kingdom,[46] and make adaptations to the URAM if necessary. The measurement properties of the recently developed SDSS should be further investigated in other populations, as it has only been used by the developers themselves. Another option is to continue the search for a PROM for use in Dupuytren patients, in which researchers, experts and Dupuytren patients from different international institutes should be involved.

In Chapter 7, the disease course of primary Dupuytren disease is described, and several factors are identified that are related to progression. The results support the clinicians' view that Dupuytren disease is progressive at the long-term. The current results provide an unique insight in the disease course and efforts should be made to continue the follow-up of this cohort.

However, since only two covariates were found to be associated with disease progression, it should be questioned whether the focus should shift from clinical and anamnestic predictors towards genetic or biological predictors. Although the first GWAS studying Dupuytren disease has been reported only 6 years ago, in the meantime there are large advances in the field of genetics and epigenetics. Epigenetics can be defined as the field studying changes in DNA-expression that occur as consequence of environmental factors, which can explain changes in phenotype in absence of changes in genotype.[72] Although research on genetic aspects of Dupuytren disease still is in its infancy, epigenetics of Dupuytren disease is a future field of study and might put risk factors of Dupuytren disease in perspective.

In addition to increasing the knowledge on the natural course of Dupuytren disease, the data of the cohort is valuable in the search for predictors of disease

course. These data may be used to develop a prediction model, which will be of great help in surgical decision-making about when to intervene. This will contribute to limiting the number of cases treated too early, or cases treated too late (see Chapter 1). Furthermore, not only the natural disease course, but also disease course after treatment should be investigated in the future. It will be interesting to see whether certain factors are associated with recurrence, in order to early identify patients with aggressive disease. Furthermore, prediction models for recurrent Dupuytren disease, that take the influence of different treatment types into account, might have a large influence on the choice of treatment. Maybe, in the future, we will be able to answer the questions why some patients experience progression and others regression, and consequently, who will benefit from aggressive treatment and who will benefit from reluctance in treatment.

CONCLUSION

This thesis provides new knowledge on various epidemiologic aspects of Dupuytren disease. Of course, the highest aim in Dupuytren research should be the prevention of the disease occurring. Small steps are taken into this direction, but there is a long road ahead. Epidemiologic studies as presented in this thesis are necessary to help focusing future studies that might eventually lead to prevention, or at least a cure.

REFERENCES

1. Hindocha S, McGrouther DA, Bayat A. Epidemiological evaluation of Dupuytren's disease incidence and prevalence rates in relation to etiology. *Hand (NY)*. 2009; 4(3): 256-269.

2. Yeh CC, Huang KF, Ho CH, et al. Epidemiological profile of Dupuytren's disease in Taiwan (Ethnic Chinese): A nationwide population-based study. *BMC Musculoskelet Disord*. 2015; 16: 20.

3. Liu Y, Chen WY. Dupuytren's disease among the Chinese in Taiwan. *J Hand Surg Am*. 1991; 16(5): 779-786.

4. Slattery D. Review: Dupuytren's disease in Asia and the migration theory of Dupuytren's disease. *ANZ J Surg*. 2010; 80(7-8): 495-499.

5. Richard-Kadio M, Yeo S, Kossoko H, Allah CK, Assi-Dje Bi Dje V. Dupuytren's contracture. A report of three cases in black Africans. *Chir Main*. 2008; 27(1): 40-42.

6. Aladin A, Oni JA. Bilateral Dupuytren's contracture in a black patient. *Int J Clin Pract*. 2001; 55(9): 641-642.

7. Gebereegziabher A, Baraki A, Kebede Y, Mohammed I, Finsen V. Dupuytren's contracture in Ethiopia. *J Hand Surg Eur Vol*. 2016; doi: 10.1177/1753193416640465.

8. McFarlane RM. On the origin and spread of Dupuytren's disease. *J Hand Surg Am*. 2002; 27(3): 385-390.

9. Werker PMN. Commentary on Dupuytren's contracture in Ethiopia. A. Gebereegziabher, A. Baraki, Y. Kebede, I. Mohammed and V. Finsen. J Hand Surg Eur. 2017, 42: 26–8. *J Hand Surg Eur Vol*. 2017; 42(1): 29.

10. Larsen S, Krogsgaard DG, Aagaard Larsen L, Iachina M, Skytthe A, Frederiksen H. Genetic and environmental influences in Dupuytren's disease: A study of 30,330 Danish twin pairs. *J Hand Surg Eur Vol*. 2015; 40(2): 171-176.

11. Dolmans GH, Wijmenga C, Ophoff RA, Werker PM. A clinical genetic study of familial Dupuytren's disease in the Netherlands. In: Eaton C., ed. *Dupuytren's disease and related hyperproliferative disorders.* 2011.

12. Furniss D, Dolmans GH, Hennies HC. Genome-wide association scan of Dupuytren's disease. *J Hand Surg Am*. 2011; 36(4): 755-756.

13. Dolmans GH, Werker PM, Hennies HC, et al. Wnt signaling and Dupuytren's disease. *N Engl J Med*. 2011; 365(4): 307-317.

14. Furniss D. Commentary on larson et al. genetic and environmental influences in Dupuytren's disease: A study of 30,330 Danish twin pairs. *J Hand Surg Eur Vol*. 2015; 40(2): 177-178.

15. Bodiga VL, Eda SR, Bodiga S. Advanced glycation end products: Role in pathology of diabetic cardiomyopathy. *Heart Fail Rev*. 2014; 19(1): 49-63.

16. Schalkwijk CG, Baidoshvili A, Stehouwer CD, van Hinsbergh VW, Niessen HW. Increased accumulation of the glycoxidation product nepsilon-(carboxymethyl)lysine in hearts of diabetic patients: Generation and characterisation of a monoclonal anti-CML antibody. *Biochim Biophys Acta*. 2004; 1636(2-3): 82-89.

17. Striker LJ, Striker GE. Administration of AGEs in vivo induces extracellular matrix gene expression. *Nephrol Dial Transplant*. 1996; 11 Suppl 5: 62-65.

18. Zhang AY, Fong KD, Pham H, Nacamuli RP, Longaker MT, Chang J. Gene expression analysis of Dupuytren's disease: The role of TGF-beta2. *J Hand Surg Eur Vol*. 2008; 33(6): 783-790.

19. Bayat A, Stanley JK, Watson JS, Ferguson MW, Ollier WE. Genetic susceptibility to Dupuytren's disease: Transforming growth factor beta receptor (TGFbetaR) gene polymorphisms and Dupuytren's disease. *Br J Plast Surg*. 2003; 56(4): 328-333.

20. Satish L, Gallo PH, Baratz ME, Johnson S, Kathju S. Reversal of TGF-beta1 stimulation of alpha-smooth muscle actin and extracellular matrix components by cyclic AMP in Dupuytren's-derived fibroblasts. *BMC Musculoskelet Disord*. 2011; 12: 113.

21. Brickley-Parsons D, Glimcher MJ, Smith RJ, Albin R, Adams JP. Biochemical changes in the collagen of the palmar fascia in patients with Dupuytren's disease. *J Bone Joint Surg Am*. 1981; 63(5): 787-797.

22. Vicens-Zygmunt V, Estany S, Colom A, et al. Fibroblast viability and phenotypic changes within glycated stiffened three-dimensional collagen matrices. *Respir Res*. 2015; 16: 82.

23. Descatha A, Carton M, Mediouni Z, et al. Association among work exposure, alcohol intake, smoking and Dupuytren's disease in a large cohort study (GAZEL). *BMJ Open*. 2014; 4(1).

24. Lanting R, van den Heuvel ER, Westerink B, Werker PM. Prevalence of Dupuytren disease in the Netherlands. *Plast Reconstr Surg*. 2013; 132(2): 394-403.

25. Burke FD, Proud G, Lawson IJ, McGeoch KL, Miles JN. An assessment of the effects of exposure to vibration, smoking, alcohol and diabetes on the prevalence of Dupuytren's disease in 97,537 miners. *J Hand Surg Eur Vol*. 2007; 32(4): 400-406.

26. Lucas G, Brichet A, Roquelaure Y, Leclerc A, Descatha A. Dupuytren's disease: Personal factors and occupational exposure. *Am J Ind Med*. 2008; 51(1): 9-15.

27. Bertrand J, Thomas J, Metman EH. Dupuytren's contracture and palmar erythema in alcoholic cirrhosis. *Sem Hop*. 1977; 53(7): 407-412.

28. Attali P, Ink O, Pelletier G, et al. Dupuytren's contracture, alcohol consumption, and chronic liver disease. *Arch Intern Med*. 1987; 147(6): 1065-1067.

29. Burge P, Hoy G, Regan P, Milne R. Smoking, alcohol and the risk of Dupuytren's contracture. *J Bone Joint Surg Br*. 1997; 79(2): 206-210.

30. Palmer KT, D'Angelo S, Syddall H, Griffin MJ, Cooper C, Coggon D. Dupuytren's contracture and occupational exposure to hand-transmitted vibration. *Occup Environ Med*. 2014; 71(4): 241-245.

31. Pojer J, Radivojevic M, Williams TF. Dupuytren's disease. its association with abnormal liver function in alcoholism and epilepsy. *Arch Intern Med*. 1972; 129(4): 561-566.

32. Critchley EM, Vakil SD, Hayward HW, Owen VM. Dupuytren's disease in epilepsy: Result of prolonged administration of anticonvulsants. *J Neurol Neurosurg Psychiatry*. 1976; 39(5): 498-503.

33. Hinz B, Mastrangelo D, Iselin CE, Chaponnier C, Gabbiani G. Mechanical tension controls granulation tissue contractile activity and myofibroblast differentiation. *Am J Pathol*. 2001; 159(3): 1009-1020.

34. Behrmann L, Litzenberger S, Mally F, Sabo A. Evaluation of bending and torsional properties of different ice hockey sticks. *Procedia Engineering*. 2014; 72: 332-337.

35. Shenoy MM, Smith LV, Axtell JT. Performance assessment of wood, metal and composite baseball bats. *Compos Struct*. 2001; 52: 397-404.

36. Van De Water L, Varney S, Tomasek JJ. Mechanoregulation of the myofibroblast in wound contraction, scarring, and fibrosis: Opportunities for new therapeutic intervention. *Adv Wound Care (New Rochelle)*. 2013; 2(4): 122-141.

37. Hinz B, Phan SH, Thannickal VJ, et al. Recent developments in myofibroblast biology: Paradigms for connective tissue remodeling. *Am J Pathol*. 2012; 180(4): 1340-1355.

38. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol*. 2002; 3(5): 349-363.

39. Gudmundsson KG, Arngrimsson R, Jonsson T. Eighteen years follow-up study of the clinical manifestations and progression of Dupuytren's disease. *Scand J Rheumatol*. 2001; 30(1): 31-34.

40. Adamietz B, Keilholz L, Grünert J, Sauer R. Radiotherapy of early stage Dupuytren disease. Long-term results after a median follow-up period of 10 years. *Strahlentherapie und Onkologie*. 2001; 177(11): 604-610.

41. Keilholz L, Seegenschmiedt MH, Sauer R. Radiotherapy for prevention of disease progression in early-stage Dupuytren's contracture: Initial and long-term results. *International Journal of Radiation Oncology*Biology*Physics*. 1996; 36(4): 891-897.

42. Ketchum LD, Donahue TK. The injection of nodules of Dupuytren's disease with triamcinolone acetonide. *J Hand Surg Am*. 2000; 25(6): 1157-1162.

43. Ball C, Pratt AL, Nanchahal J. Optimal functional outcome measures for assessing treatment for Dupuytren's disease: A systematic review and recommendations for future practice. *BMC Musculoskelet Disord*. 2013; 14: 131.

44. Engstrand C, Krevers B, Kvist J. Interrater reliability in finger joint goniometer measurement in Dupuytren's disease. *Am J Occup Ther*. 2012; 66(1) :98-103.

45. Lo S, Pickford M. Current concepts in Dupuytren's disease. *Curr Rev Musculoskelet Med*. 2013; 6(1): 26-34.

46. Rodrigues JN, Zhang W, Scammell BE, Davis TR. What patients want from the treatment of Dupuytren's disease - is the Unité Rhumatologique des Affections de la Main (URAM) scale relevant? *J Hand Surg Eur Vol*. 2015; 40(2): 150-154.

47. Mohan A, Vadher J, Ismail H, Warwick D. The Southampton Dupuytren's Scoring Scheme. *J Plast Surg Hand Surg*. 2014; 48(1): 28-33.

48. Beaudreuil J, Allard A, Zerkak D, et al. Unité Rhumatologique des Affections de la Main (URAM) scale: Development and validation of a tool to assess Dupuytren's disease-specific disability. *Arthritis Care Res.* 2011; 63(10): 1448-1455.

49. Lanting R, van den Heuvel ER, Werker PM. Clusters in short-term disease course in participants with primary Dupuytren disease. *J Hand Surg Am*. 2016; 41(3): 354-361.

50. Rayan GM. Dupuytren's disease vs non-Dupuytren's contracture. *J Hand Surg Am*. 2005; 30(5): 1019-1020.

51. Degreef I, De Smet L. Risk factors in Dupuytren's diathesis: Is recurrence after surgery predictable? *Acta Orthop Belg*. 2011; 77(1): 27-32.

52. Hindocha S, Stanley JK, Watson S, Bayat A. Dupuytren's diathesis revisited: Evaluation of prognostic indicators for risk of disease recurrence. *J Hand Surg Am*. 2006; 31(10): 1626-1634.

53. Kaufmann H, Norcliffe-Kaufmann L, Palma JA, et al. Natural history of pure autonomic failure: A united states prospective cohort. *Ann Neurol*. 2017; 81(2): 287-297.

54. Kugathasan S, Denson LA, Walters TD, et al. Prediction of complicated disease course for children newly diagnosed with Crohn's disease: A multicentre inception cohort study. *Lancet*. 2017.

55. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. *Head Neck*. 2015; 37(11): 1625-1632.

56. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: A population-based cohort study. *Gastroenterology*. 2008; 135(4): 1106-1113.

57. Kan HJ, Selles RW, van Nieuwenhoven CA, Zhou C, Khouri RK, Hovius SE. Percutaneous aponeurotomy and lipofilling (PALF) versus limited fasciectomy in patients with primary Dupuytren's contracture: A prospective, randomized, controlled trial. *Plast Reconstr Surg*. 2016; 137(6): 1800-1812.

58. Zhou C, Hovius SE, Slijper HP, et al. Collagenase clostridium histolyticum versus limited fasciectomy for Dupuytren's contracture: Outcomes from a multicenter propensity score matched study. *Plast Reconstr Surg*. 2015; 136(1): 87-97.

59. Bainbridge C, Gerber RA, Szczypa PP, et al. Efficacy of collagenase in patients who did and did not have previous hand surgery for Dupuytren's contracture. *J Plast Surg Hand Surg*. 2012; 46(3-4): 177-183.

60. Yan HD, Li XZ, Xie JM, Li M. Effects of advanced glycation end products on renal fibrosis and oxidative stress in cultured NRK-49F cells. *Chin Med J (Engl)*. 2007; 120(9): 787-793.

61. van Heerebeek L, Hamdani N, Handoko ML, et al. Diastolic stiffness of the failing diabetic heart: Importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation*. 2008; 117(1): 43-51.

62. Han J, Tan C, Wang Y, Yang S, Tan D. Betanin reduces the accumulation and cross-links of collagen in high-fructose-fed rat heart through inhibiting non-enzymatic glycation. *Chem Biol Interact*. 2015; 227: 37-44.

63. Schwenger V, Morath C, Salava A, et al. Damage to the peritoneal membrane by glucose degradation products is mediated by the receptor for advanced glycation end-products. *J Am Soc Nephrol*. 2006; 17(1): 199-207.

64. Koetsier M, Lutgers HL, de Jonge C, Links TP, Smit AJ, Graaff R. Reference values of skin autofluorescence. *Diabetes Technol Ther.* 2010; 12(5): 399-403.

65. Stern CS, Schreiber JE, Surek CL, et al. 3D topographical surface changes in response to compartmental volumization of the medial cheek; defining a malar "augmentation zone". *Plast Reconstr Surg*. 2016; 137(5): 1401-1408.

66. Koch MC, Adamietz B, Jud SM, et al. Breast volumetry using a three-dimensional surface assessment technique. *Aesthetic Plast Surg*. 2011; 35(5): 847-855.

67. Robertson SA, Kimble RM, Storey KJ, Gee Kee EL, Stockton KA. 3D photography is a reliable method of measuring infantile haemangioma volume over time. *J Pediatr Surg*. 2016; 51(9): 1552-1556.

68. Stockton KA, McMillan CM, Storey KJ, David MC, Kimble RM. 3D photography is as accurate as digital planimetry tracing in determining burn wound area. *Burns*. 2015; 41(1): 80-84.

69. Gee Kee EL, Kimble RM, Stockton KA. 3D photography is a reliable burn wound area assessment tool compared to digital planimetry in very young children. *Burns*. 2015; 41(6): 1286-1290.

70. Creteur V, Madani A, Gosset N. Ultrasound imaging of Dupuytren's contracture. *J Radiol*. 2010; 91(6): 687-691.

71. Yacoe ME, Bergman AG, Ladd AL, Hellman BH. Dupuytren's contracture: MR imaging findings and correlation between MR signal intensity and cellularity of lesions. *AJR Am J Roentgenol*. 1993; 160(4): 813-817.

72. Holliday R. The inheritance of epigenetic defects. *Science*. 1987; 238(4824): 163-170.

Appendix 8.1. Point estimates [95% CI] of prevalence of Dupuytren disease, reported for the total population as well as for men and women separately [derived from Chapter 2, Figure 2].

Prevalence in percentages [95% CI]			
Age	***Totals***	***Men***	***Women***
25	0.133 [0.066 ; 0.266]	0.568 [0.273 ; 1.168]	0.002 [0.000 ; 0.019]
30	0.405 [0.206 ; 0.789]	1.280 [0.605 ; 2.651]	0.010 [0.001 ; 0.081]
35	1.026 [0.515 ; 2.012]	2.497 [1.166 ; 5.117]	0.039 [0.005 ; 0.284]
40	2.242 [1.094 ; 4.419]	4.337 [2.028 ; 6.824]	0.132 [0.019 ; 0.856]
45	4.302 [2.055 ; 8.346]	6.836 [3.245 ; 12.972]	0.380 [0.058 ; 2.211]
50	7.331 [3.494 ; 13.634]	9.924 [4.845 ; 17.795]	0.955 [0.150 ; 4.763]
55	11.231 [5.460 ; 19.666]	13.442 [6.818 ; 22.725]	2.090 [0.339 ; 8.476]
60	15.707 [7.929 ; 25.782]	17.198 [9.119 ; 27.496]	3.975 [0.689 ; 12.814]
65	20.406 [10.808 ; 31.555]	21.012 [11.675 ; 31.960]	6.588 [1.268 ; 17.231]
70	25.045 [13.962 ; 36.800]	24.751 [14.399 ; 36.056]	9.683 [2.168 ; 21.427]
75	29.449 [17.251 ; 41.484]	28.329 [17.209 ; 39.778]	12.959 [3.396 ; 25.299]
80	33.535 [20.554 ; 45.639]	31.697 [20.032 ; 43.146]	16.199 [4.941 ; 28.833]
85	37.279 [23.783 ; 49.323]	34.839 [22.813 ; 46.190]	19.284 [6.734 ; 32.050]
90	40.689 [26.881 ; 52.595]	37.751 [25.512 ; 48.945]	22.171 [8.684 ; 34.982]
95	43.790 [29.816 ; 55.514]	40.444 [28.104 ; 51.444]	24.850 [10.702 ; 37.661]
100	46.611 [32.576 ; 58.128]	42.931 [30.573 ; 53.718]	27.329 [12.723 ; 40.116]

CI: confidence interval.