Epidemiology of Dupuytren disease unraveled

Broekstra, Dieuwke

GENERAL INTRODUCTION AND OUTLINE

Dupuytren disease: etiology and epidemiology

Dupuytren disease is a connective tissue disease affecting the palmar fascias of the hand. It has been named after the French surgeon and anatomist Guillaume Dupuytren. Early signs of this disease are skin pitting, and the presence of nodules (Figure 1A). Usually, a nodule is a firm lump, commonly located in the palm of the hand, that mainly consists of collagen and (myo)fibroblasts.[1,2] Myofibroblasts are fibroblasts that contain a contractile element. Mostly, nodules are painless and do not lead to functional complaints. Therefore, they are not always recognized by the patient, as indicated by a previous study of our research group on prevalence,[3] in which many of the participants having mild disease reported that they did not notice the small nodules. The nodules can progress into cords, in which the cellular density is decreased and the myofibroblasts are aligned along the lines of mechanical stress.[4] Contraction of myofibroblasts in combination with synthesis and degradation of extra-cellular matrix, results in connective tissue remodeling. This interplay eventually gives rise to the characteristic flexion contracture of the fingers (Figure 1B). The flexion contractures can cause functional complaints, or even lead to psychosocial complaints, as it may impede the patients' self-esteem.[5] Even though Dupuytren disease is considered as a benign disease, underlying mechanisms as abnormal Wnt signaling[6] or molecular alterations,[4] and features such as a high likelihood of recurrence after treatment, with lower recurrence rates after rigorous treatment, have similarities with neoplastic diseases.[7] Previously, it has been suggested that Dupuytren disease is associated with a higher mortality,[8-10] and this has recently been supported by results of a large cohort study.[11]

It is unknown what exactly triggers the transformation of fibroblasts in the palmar fascia into myofibroblasts, but there is evidence that it is associated with cell stress and several molecular changes. These include an increased level of growth factors,[12-14] cytokines,[12] extra-cellular related proteins,[15,16] and altered levels of matrix-metalloproteinases,[17,18] combined with altered levels of tumor necrosis factor.[19] These alterations are also present in inflammation and scar formation.[20,21]

The reported prevalence of Dupuytren disease varies largely, from 0.6 to 56.0%.[22] Possible causes for this broad range are the different populations studied (e.g. some

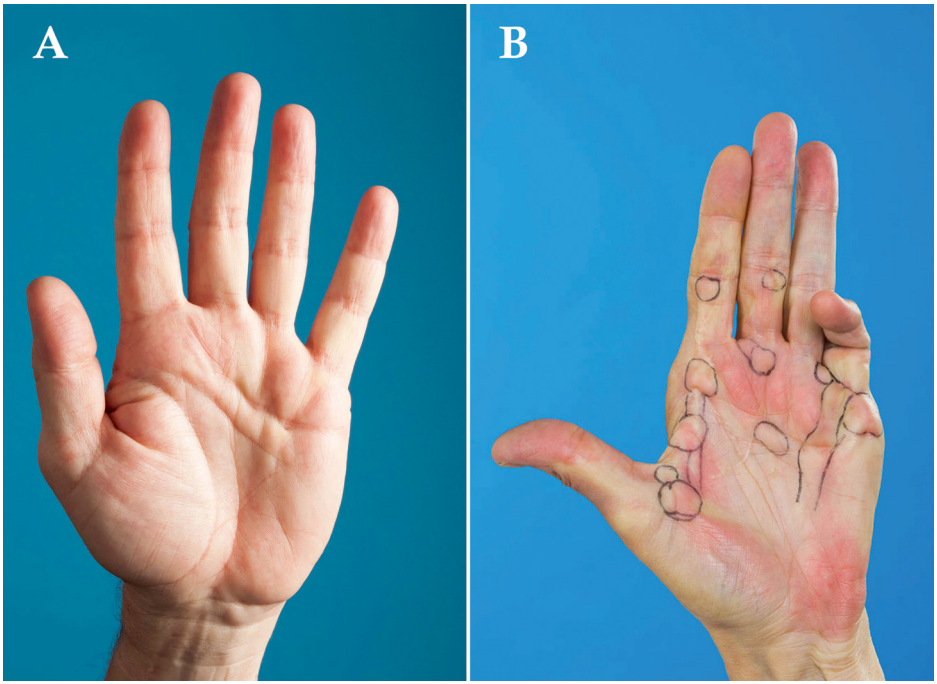

Figure 1. A) Mild stage of Dupuytren disease, in which a nodule is present in the ring finger ray in the palm of the hand. B) Severe stage of Dupuytren disease, in which a contracture of the little finger ray is present, and multiple nodules and cords in the first web space, palm and fingers have been encircled.

studies only included patient groups, while others studied general populations), differences in genetic predisposition between populations of different countries, or suboptimal study design of the prevalence studies. Research performed in the general elderly population of Groningen (the Netherlands), has shown that the prevalence is 22.1% in people over 50 years of age.[3] Men are more frequently affected than women.[3,23] As the prevalence tends to rise with increasing age,[3,23] Dupuytren disease can be seen as a chronic disease of the elderly. This may, in the coming decades, lead to increased health care costs related to the treatment of this disease. Because of this, a reliable estimation of the prevalence of Dupuytren disease in the general population worldwide, is important.

Although the influence of many suspected risk factors has not yet been elucidated, genome wide association studies (GWAS) and twin studies have shown that

genetics play an important role.[6,24,25] Beside this, several other intrinsic and extrinsic risk factors are frequently linked to Dupuytren disease in the literature. Examples of intrinsic risk factors are diabetes mellitus, epilepsy and liver disease. These conditions are often studied in relation with Dupuytren disease, but a statistically significant association has not always been confirmed.[26-29] Examples of extrinsic risk factors that are often suggested to be related with Dupuytren disease, are exposure to manual work and hand-arm vibrations.[30-33] Several studies have been done on this topic, but again, a statistically significant association was not always found. Almost all studies that investigated the association between Dupuytren disease and vibration, focused on occupational exposure to vibration.[29,31,33] However, vibration exposure can also occur during leisure or sports activities.[34,35] To date, this has never been subject of study.

Treatment options

Dupuytren disease cannot be cured, so treatment is aimed at preventing disease progression or reducing the flexion contractures of the fingers. Some claim that the former can be achieved by radiation therapy that prevents the proliferation of fibroblasts,[36,37] by anti-inflammatory drugs,[38,39] or by the estrogen receptor antagonist tamoxifen,[40] although the evidence for the effectiveness of these methods is limited. Recently, a possible new therapeutic target has been identified, i.e. tumor necrosis factor, that might prevent disease progression.[19]

Flexion contractures can be corrected using different treatment options, such as surgery, in which the cord is transsected or resected, or collagenase injections that lead to local breakdown of the Dupuytren cord. Although collagenase injections replaced part of the surgical procedures in the United States,[41,42] most patients in the Netherlands are still treated surgically with percutaneous needle fasciotomy or limited fasciectomy, because collagenase treatment is not being reimbursed by the insurance companies.[43] In percutaneous needle fasciotomy, the Dupuytren cord is divided with a needle, whereafter the finger (in most cases) can be extended. The dissected cord is not removed using this technique. In limited fasciectomy, the diseased tissue is removed, sometimes combined with removal of the overlying skin (dermofasciectomy). A skin graft is used to close the defect that occurs as consequence of the dermofasciectomy.

Unfortunately, recurrences are common and many patients require treatment again.[7] This is a challenge in surgical treatment of Dupuytren disease, since the scar tissue itself (that remains after surgical treatment) may form a source for the formation of new Dupuytren nodules and cords.[20,21] In extreme cases, amputation of the affected ray is the only treatment option that is left to regain functional ability. With this in mind, it is evident that timing of surgical treatment is essential. Treating too early might result in multiple recurrences or earlier recurrences.[44] However, treating too late can make the treatment less successful, because of larger contracture deformities involving multiple joints, an increased chance of natural arthrodesis due to flexion contractures, and because of increased surgical complexity.

Disease course

Despite the fact that this disease has been described as early as in the 17th century by Felix Platter, literature on the course of Dupuytren disease is scarce. One study describes the results of fasciectomy and fasciotomy with a follow-up time of 5 years, and the results are compared to a control group of Dupuytren patients who received no treatment.[45] Unfortunately, the sample size in this study is small (47 untreated hands, and the number of participants is not reported) and no statistical analyses have been done, which hampers the interpretation of the results.

The prevailing thought from a clinical point of view is that Dupuytren disease is progressive. However, experience shows there are also cases in which the disease is stable, or even in regression.[46] This difference might be explained by the sampling method. In the vast majority of studies, participants are recruited from a hospital population. As a consequence, only patients with a more severe form of Dupuytren disease are included. The mild cases, in which only nodules are present, may not seek medical advice. So, they are less likely to be included in a study. Additionally, the few other studies that were done to determine the disease course, only used two measurement times.[28,46] In this way, only a linear disease course profile could be estimated. Precise knowledge about the disease course is important to gain insight in the development of the disease, but more importantly, to identify factors that may trigger disease progression, and to facilitate the clinicians' decision about when to treat best.

Therefore, a cohort-study was designed, in which patients with various stages

of Dupuytren disease were followed-up every 6 months, to evaluate the course of primary Dupuytren disease. After 1.5 years, interim-analyses were done. Three clinically different disease courses were identified, namely progression, stability and regression. In the majority of the participants, the disease was stable. Disease extent (surface area of the nodules and cords in a ray) at the start of the study was associated with disease course.[47] So, the larger the disease extent, the larger the chance to have progressive disease. There were no other risk factors that could explain why some experienced progression, and others did not. An explanation might be that the change due to progression was too small to be discriminated from variability in measurements. Therefore, a description of long-term (more than 1.5 years) disease course of Dupuytren disease may be needed to identify risk factors for progression.

Outcome measures in research on Dupuytren disease

The most commonly used outcome measure in Dupuytren research is range of motion, and especially extension deficit, which is the inability to straighten the fingers.[48] It can be measured either active or passive, and both types are used in the literature.[7,49,50] The extension deficit is measured in each finger joint separately, but it can be summed to form a total passive or active extension deficit per finger. Although this variable is considered as the most suitable objective outcome measure for quantifying severity and treatment effects, the reliability of this outcome is unclear. Furthermore, it has some disadvantages in statistical analysis, that will be explained later. Another disadvantage is that it cannot be measured in patients who only have mild Dupuytren disease without flexion contractures. Therefore, we searched for an alternative measure. In such patients, we used the surface area of nodules and cords, measured with a tumorimeter. This is a planimeter that is used in oncology to measure the surface area of tumors on X-rays.[51] The surface area was used as alternative measure for quantifying disease extent.

As mentioned before, previous studies have mainly focused on extension deficit as outcome measure in Dupuytren research. The patient's perspective has long been neglected. Lately, a few studies have appeared studying hand function and quality of life in patients with Dupuytren disease.[52,53] Despite the increasing attention to the patient's opinion, there is no patient reported outcome measure (PROM) that

is universally used. Additionally, all the available PROMs are designed to detect change after treatment. It is unclear whether the PROMs are able to detect change over time due to disease progression. This needs to be elucidated before the PROM can be used in clinical practice to determine the functional consequences of disease progression.

Data-analysis of outcome measures

As stated in the previous section, measuring extension deficits has some important consequences for the statistical data-analysis.

First, extension deficit is often measured in all finger joints, and in multiple fingers per participant. This results in multiple observations within one participant. Clearly, these observations cannot be considered independent, which is an assumption of many statistical tests. The data contain a multilevel structure, as is shown in Figure 2. This multilevel structure of the data poses some challenges when it comes to analyzing the data, and ignoring it can lead to wrong conclusions.[54]

There are several methods to manage multilevel data statistically. First of all, commonly used statistical software packages contain techniques such as generalized linear mixed-effects models that are designed to analyze multilevel data. If the use of these models is not possible, another solution is to reduce the number of levels in the dataset by processing parameters: for example, passive extension deficits that are measured in the three different finger joints can be added together to form a total passive extension deficit. By doing this, one level has been eliminated (joint). Further reduction of the number of levels can be done by randomly selecting one finger per participant which is included in the analysis, instead of including multiple fingers per participant in the analysis. It is important to note that as a consequence, data are lost after data reduction, so this is not always a preferable option.

Secondly, extension deficit (regardless of whether it is active, passive, or total) is often a zero-inflated continuous parameter, which means that the parameter shows clustering at zero, since most patients do not have contractures anymore once they have been treated. It is also possible that there are Dupuytren disease patients in the study who do not have contractures at all, resulting in an extension deficit of zero. Therefore, the distribution of this outcome measure is not normal. Data transformation to obtain normality is also not possible, since no calculations

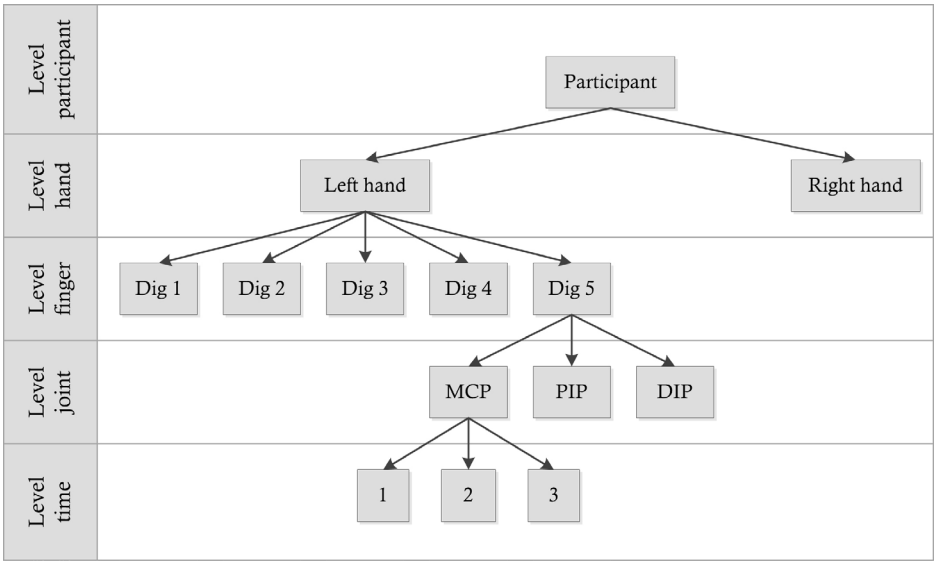

Figure 2. An example of the data structure of a Dupuytren dataset containing multiple levels. Note that the different levels are only presented for the MCP of the left fifth digit, to limit the size of the figure. Dig: digit; MCP: metacarpophalangeal joint; PIP: proximal interphalangeal joint; DIP: distal interphalangeal joint.

can handle large numbers of zero. A possibility to analyze this type of outcome measure is to use a mixture distribution. A mixture distribution can be considered as a combination of only parametric distributions, or as combination of a parametric and a non-parametric distribution (or distribution free). The zero-inflated data can be analyzed with the parametric model, while the positive values would be modeled with the non-parametric component. This way, the parametric and non-parametric components that frequently characterize extension deficit measurements, can be analyzed together. However, in practice the non-parametric part is often replaced by a normal or lognormal distribution.

Thirdly, measuring outcomes at multiple moments in time yields an additional level in the multilevel structure of the data (Figure 2). Although paired t-tests and repeated measures analysis of variance (RM ANOVA) can be used for two or more measurements, these techniques are often not applicable due to non-normality of the data. In some cases, the difference score between two measurements might be normally distributed, and can be used as outcome. Another limitation of t-tests, RM

ANOVA, and non-parametric equivalents, is that they can only handle two levels in the data. Generalized linear mixed-effects models provide much a more flexible statistical technique, that, at this moment, is the most suitable technique that is available to analyze data in Dupuytren research.

Aim of this thesis

It is clear that Dupuytren disease is a developing field of study, according to the increase of papers that have been published on Dupuytren disease in the last decades.[55] Despite this, there are many epidemiological and methodological aspects left to unravel. Therefore, the general aim of this thesis is to gain more insight into prevalence, risk factors and disease course of Dupuytren disease. In addition, some considerations on the methodology are addressed.

Outline of this thesis

Part I. Prevalence and risk factors

To narrow the prevalence range of Dupuytren disease reported in the literature, a systematic review and meta-analysis on the prevalence of Dupuytren disease in the general population was done. The results are presented in **Chapter 2**, in which prevalence rates including prediction intervals are presented as function of age and sex. In an attempt to end the ongoing debate about the association between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy, the strength and consistency of previously reported associations was studied in a systematic review and meta-analysis (**Chapter 3**). Furthermore, we studied the influence of sports activities with hand-held devices on the presence of Dupuytren disease, which was examined in **Chapter 4**. In this chapter, the results of a large cross-sectional study are reported in which the association between field-hockey playing and Dupuytren disease was determined.

Part II. Considerations on the measurement methods

As the reliability of the most frequently used outcome measure in Dupuytren research is unknown, **Chapter 5** covers the inter- and intra-observer reliability of diagnosis and finger goniometry in patients with Dupuytren disease. A new measurement method is introduced as well, to determine disease progression in

participants with mild disease: a tumorimeter. Furthermore, various PROMs are used in Dupuytren research, but it has never been investigated whether the PROMs are able to detect change in hand function as result of Dupuytren disease progression. This was determined in **Chapter 6**, in which the Dutch language version of the Unité Rhumatologique des Affection de la Main (URAM) was validated and its ability to assess change in hand function due to disease progression was compared to the Michigan Hand Questionnaire (MHQ).

Part III. Natural disease course of Dupuytren disease

To provide a detailed description of the long-term natural disease course of primary Dupuytren disease as function over time, the 4.5 year results of the previously described cohort study are presented in **Chapter 7**. In this chapter, prospectively gathered data of 258 participants with Dupuytren disease was examined to describe the natural disease course of untreated Dupuytren disease. Additionally, we tried to find risk factors for disease progression.

Chapter 8 provides a critical discussion of the findings in this thesis, and places the results in a wider context. Next to that, future perspectives are also presented in this chapter.

REFERENCES

1. Gabbiani G, Majno G. Dupuytren's contracture: Fibroblast contraction? An ultrastructural study. *Am J Pathol.* 1972; 66(1): 131-146.

2. Bailey AJ, Sims TJ, Gabbiani G, Bazin S, LeLous M. Collagen of Dupuytren's disease. *Clin Sci Mol Med.* 1977; 53(5): 499-502.

3. 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.

4. Shih B, Bayat A. Scientific understanding and clinical management of Dupuytren disease. *Nat Rev Rheumatol.* 2010; 6(12): 715-726.

5. Wilburn J, McKenna SP, Perry-Hinsley D, Bayat A. The impact of Dupuytren disease on patient activity and quality of life. *J Hand Surg Am.* 2013; 38(6): 1209-1214.

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

7. van Rijssen AL, ter Linden H, Werker PM. Five-year results of a randomized clinical trial on treatment in Dupuytren's disease: Percutaneous needle fasciotomy versus limited fasciectomy. *Plast Reconstr Surg.* 2012; 129(2): 469-477.

8. Mikkelsen OA, Hoyeraal HM, Sandvik L. Increased mortality in Dupuytren's disease. *J Hand Surg Br.* 1999; 24(5): 515-518.

9. Gudmundsson KG, Arngrimsson R, Sigfusson N, Jonsson T. Increased total mortality and cancer mortality in men with Dupuytren's disease: A 15-year follow-up study. *J Clin Epidemiol.* 2002; 55(1): 5-10.

10. Wilbrand S, Ekbom A, Gerdin B. A cohort study linked increased mortality in patients treated surgically for Dupuytren's contracture. *J Clin Epidemiol*. 2005; 58(1): 68-74.

11. Kuo R, Prieto-Alhambra D, Furniss D. Dupuytren disease predicts increased cancer and cardiovascular mortality. *Hand.* 2016; 11(1 suppl): 18S-19S.

12. Baird KS, Crossan JF, Ralston SH. Abnormal growth factor and cytokine expression in Dupuytren's contracture. *J Clin Pathol.* 1993; 46(5): 425-428.

13. Gonzalez AM, Buscaglia M, Fox R, et al. Basic fibroblast growth factor in Dupuytren's contracture. *Am J Pathol.* 1992; 141(3): 661-671.

14. Badalamente MA, Hurst LC, Grandia SK, Sampson SP. Platelet-derived growth factor in Dupuytren's disease. *J Hand Surg Am.* 1992; 17(2): 317-323.

15. Lee LC, Zhang AY, Chong AK, Pham H, Longaker MT, Chang J. Expression of a novel gene, MafB, in Dupuytren's disease. *J Hand Surg Am.* 2006; 31(2): 211-218.

16. Degreef I, De Smet L, Sciot R, Cassiman JJ, Tejpar S. Beta-catenin overexpression in Dupuytren's disease is unrelated to disease recurrence. *Clin Orthop Relat Res.* 2009; 467(3): 838-845.

17. Johnston P, Larson D, Clark IM, Chojnowski AJ. Metalloproteinase gene expression correlates with clinical outcome in Dupuytren's disease. *J Hand Surg Am.* 2008; 33(7): 1160-1167.

18. Ulrich D, Ulrich F, Piatkowski A, Pallua N. Expression of matrix metalloproteinases and their inhibitors in cords and nodules of patients with Dupuytren's disease. *Arch Orthop Trauma Surg.* 2009; 129(11): 1453-1459.

19. Verjee LS, Verhoekx JS, Chan JK, et al. Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target. *Proc Natl Acad Sci USA*. 2013; 110(10): E928-937.

20. Howard JC, Varallo VM, Ross DC, et al. Wound healing-associated proteins Hsp47 and fibronectin are elevated in Dupuytren's contracture. *J Surg Res*. 2004; 117(2): 232-238.

21. Cheon SS, Cheah AY, Turley S, et al. Beta-catenin stabilization dysregulates mesenchymal cell proliferation, motility, and invasiveness and causes aggressive fibromatosis and hyperplastic cutaneous wounds. *Proc Natl Acad Sci USA.* 2002; 99(10): 6973-6978.

22. 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.

23. Gudmundsson KG, Arngrimsson R, Sigfusson N, Bjornsson A, Jonsson T. Epidemiology of Dupuytren's disease: Clinical, serological, and social assessment. The Reykjavik study. *J Clin Epidemiol*. 2000; 53(3): 291-296.

24. Ng M, Zeggini E, Hennies HC, Werker PM, Furniss D. Dissecting the development of Dupuytren disease through human genetics. *Hand*. 2016; 11(1 suppl): 20S.

25. 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.

26. 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.

27. Geoghegan JM, Forbes J, Clark DI, Smith C, Hubbard R. Dupuytren's disease risk factors. *J Hand Surg Br.* 2004; 29(5): 423-426.

28. Reilly RM, Stern PJ, Goldfarb CA. A retrospective review of the management of Dupuytren's nodules. *J Hand Surg Am.* 2005; 30(5): 1014-1018.

29. 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.

30. Seidler A, Stolte R, Nienhaus A, Windolf J, Elsner G. Occupational, consumption-related and disease-related risk factors for Dupuytren's contracture: Results of a case-control study. *Arbeitszmedizin Sozialmedizin Umweltmedizin.* 2001; 36(5): 218-229.

31. 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.

32. Bovenzi M. Hand-arm vibration syndrome and dose-response relation for vibration induced white finger among quarry drillers and stonecarvers. Italian study group on physical hazards in the stone industry. *Occup Environ Med.* 1994; 51(9): 603-611.

33. 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).

34. Roberts JR, Jones R, Mansfield NJ, Rothberg SJ. Evaluation of vibrotactile sensations in the 'feel' of a golf shot. *J Sound Vibrat.* 2005; 285(1-2): 303-319.

35. Russell DA. Flexural vibration and the perception of sting in hand-held sports implements. 41st International Congress and Exposition on Noise Control Engineering. 2012; 12.

36. Herbst M, Regler G. Dupuytrensche kontraktur. *Strahlentherapie.* 1986; 161: 143-147.

37. Seegenschmiedt MH, Olschewski T, Guntrum F. Radiotherapy optimization in early-stage Dupuytren's contracture: First results of a randomized clinical study. *Int J Radiat Oncol Biol Phys.* 2001; 49(3): 785-798.

38. Meek RM, McLellan S, Reilly J, Crossan JF. The effect of steroids on Dupuytren's disease: Role of programmed cell death. *J Hand Surg Br.* 2002; 27(3): 270-273.

39. Pittet B, Rubbia-Brandt L, Desmouliere A, et al. Effect of gamma-interferon on the clinical and biologic evolution of hypertrophic scars and Dupuytren's disease: An open pilot study. *Plast Reconstr Surg.* 1994; 93(6): 1224-1235.

40. Degreef I, Tejpar S, Sciot R, De Smet L. High-dosage tamoxifen as neoadjuvant treatment in minimally invasive surgery for Dupuytren disease in patients with a strong predisposition toward fibrosis: A randomized controlled trial. *J Bone Joint Surg Am.* 2014; 96(8): 655-662.

41. Lipman MD, Carstensen SE, Deal DN. Trends in the treatment of Dupuytren disease in the United States between 2007 and 2014. *Hand.* 2017; 12(1): 13-20.

42. Zhao JZ, Hadley S, Floyd E, Earp BE, Blazar PE. The impact of collagenase clostridium histolyticum introduction on Dupuytren treatment patterns in the United States. *J Hand Surg.* 2016; 41(10): 963-968.

43. van Rijssen AL, Werker PM. Treatment of Dupuytren's contracture; an overview of options. *Ned Tijdschr Geneeskd.* 2009; 153: A129.

44. Balaguer T, David S, Ihrai T, Cardot N, Daideri G, Lebreton E. Histological staging and Dupuytren's disease recurrence or extension after surgical treatment: A retrospective study of 124 patients. *J Hand Surg Eur Vol.* 2009;3 4(4): 493-496.

45. Rodrigo JJ, Niebauer JJ, Brown RL, Doyle JR. Treatment of Dupuytren's contracture. long-term results after fasciotomy and fascial excision. *J Bone Joint Surg Am.* 1976; 58(3): 380-387.

46. 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.

47. 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.

48. 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.

49. 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.

50. Brauns A, Van Nuffel M, De Smet L, Degreef I. A clinical trial of tension and compression orthoses for Dupuytren contractures. *J Hand Ther.* 2017. doi: 10.1016/j.jht.2016.11.011

51. Dorr RT, Alberts DS. Quantitation of ellipsoid tumor areas using a circumferential measuring device. *Med Oncol Tumor Pharmacother.* 1988; 5(4): 249-251.

52. Engstrand C, Krevers B, Nylander G, Kvist J. Hand function and quality of life before and after fasciectomy for Dupuytren contracture. *J Hand Surg Am.* 2014; 39(7): 1333-1343.

53. Dias JJ, Braybrooke J. Dupuytren's contracture: An audit of the outcomes of surgery. *J Hand Surg Br*. 2006; 31(5): 514-521.

54. Sauerland S, Lefering R, Bayer-Sandow T, Bruser P, Neugebauer EA. Fingers, hands or patients? The concept of independent observations. *J Hand Surg Br*. 2003; 28(2): 102-105.

55. National Center for Biotechnology Information (NCBI)[Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; [1988] - [cited 2017 May 16]. Available from: https://www.ncbi.nlm.nih.gov/pubmed?term=%22Dupuytren+Contracture%22[Mesh]

Part I

Prevalence and risk factors