CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THESIS

General introduction and outline of thesis

Dupuytren's disease is a fibroproliferative disease of the palmar fascias of the hand. The disease was named after Guillaume Dupuytren, who was one of the first to demonstrate an operation of a patient with Dupuytren's disease in 1831 and whose demonstrating was transcripted and spread by his students, giving a detailed anatomical and pathological description of the disease (1).

Usually the disease starts with the formation of small nodules or pits in the palm, which are mostly asymptomatic and are often overlooked by patients (2). In an early stage, the nodules mainly consist of myofibroblasts, which are fibroblasts containing a contractile element (3). When the disease progresses, the myofibroblasts align along the lines of tension and eventually devolve into a tendon-like cord extending to the fingers, consisting mainly of type-III collagen (4,5). These cords may contract and lead to contractures of the affected finger joints. Because of these contractures patients are unable to fully extend the affected fingers, which causes functional complaints (6). Even trivial activities like shaking hands or putting on gloves can become a daily challenge.

Dupuytren's disease particularly occurs in the Northern parts of Europe (7-9). Many studies have described the prevalence of Dupuytren's disease in European and other Western countries, which in a meta-analysis was found to range from 0.6% to 31.6% (10). In a study from the northern part of the Netherlands among the general population, the overall prevalence was 22.1% in people older than 50 years, with much higher figures in the older age groups (11). The aetiology of Dupuytren's disease has been studied extensively and many risk-factors seem to play a role. Dupuytren's disease is more common in males and, as mentioned previously, the prevalence increases with age (7,12). Genome wide association studies and twin studies show that there is a clear genetic component, with a heritability of 80% (13-15). Furthermore, several co-morbidities have been associated with the disease, although previous literature has not always been consistent. A recent systematic review and meta-analysis demonstrated a strong association between Dupuytren's disease and diabetes mellitus and also an association between Dupuytren's disease and liver disease and epilepsy (16). In another recent systematic review this strong association between Dupuytren's disease and diabetes mellitus was confirmed. However, evidence on the association between Dupuytren's disease and liver disease and epilepsy was weak or inconclusive (17). Other, extrinsic, factors have also been related to Dupuytren's disease, including manual labour and hand trauma (18-20). The association between these possible risk-factors and Dupuytren's disease has to be investigated more thoroughly.

Despite several risk factors that have been associated with the development of Dupuytren's disease, the disease course remains extremely variable (21-23). In 1963, Hueston described a pattern of bilateral disease, clear familial trade and exhibition of ectopic disease (Ledderhose disease of the feet, Peyronie disease of the penis and/or Garrods knuckle pads), which would predispose a patient to an aggressive disease course. These characteristics were coined the "Dupuytren's diathesis" (24). Although these patients form the biggest challenge for surgeons, a prevalence study from the northern parts of the Netherlands showed that most patients that were diagnosed with Dupuytren's disease, only had palmar nodules, contractures were rarely seen (11). The overall thought is that Dupuytren's disease is progressive. However, most studies that have found this, recruited patients from a hospital population, which only is the tip of the Dupuytren's disease iceberg. The majority of cases probably do not experience significant complaints and therefore do not seek medical help. In a prospective cohort study, participants from both the "subclinical" population and the hospital population were followed for a period of 20 months, with intervals of 6 months (22). The results of this study showed that Dupuytren's disease is not always progressive and that most patients have stable disease on the short-term. No risk factors that explained why some participants experienced progression and others did not, could be found. On the long term, after a 4.5-year follow-up period, Dupuytren's disease was progressive, when looking at area of disease and total passive extension deficit (TPED). Only patients with Ledderhose disease and patients from the hospital population had a higher risk of progression. No other clinical and anamnestic factors were (consistently) associated with progression (23).

Treatment options

Numerous treatment options have been described for Dupuytren's disease. However, as Dupuytren's disease is a chronic disease, there is no available treatment that aims at a definite cure. Treatment options range from non- to minimally to highly invasive. The mainstay of treatment for patients with established flexion contractures is still surgery. Currently, limited fasciectomy is most commonly used, which aims at reducing contractures by locally removing Dupuytren's tissue in affected rays (25). The most invasive approach is dermofasciectomy, which involves excision of the cord, together with the overlying affected skin of the proximal phalanx (26). This treatment is reserved for patients having recurrence, that are at risk of multiple recurrences. Over the past decades, less invasive methods for the reduction of contractures have entered the stage. With percutaneous needle fasciotomy (PNF) or collagenase clostridium hystoliticum (CCH) injections, cords can be weakened locally using a sharp needle or by enzymatic lysis (27,28). After this, some force is applied to fully interrupt the cord, hereby extending the finger. The efficacy of these methods is satisfactory, but there is a higher risk of recurrence than with invasive procedures (29,30).

As the risk of recurrence following surgery is high, and the risk of complications and poor functional outcome increases with recurrent operations, the ultimate goal is to develop a uniformly successful non-surgical treatment that aims at early control of Dupuytren's disease or even at regression (12,31,32). This is especially of importance for patients with a suspected aggressive course of the disease, who are at risk of undergoing multiple operations that can ultimately lead to finger amputations, due to severe functional deficits or vascular injury (33,34). A variety of non-invasive treatment options that aim at early disease control have been described (35,36). Unfortunately most of the evidence is weak or absent (35). Radiotherapy is believed to control the development of myofibroblasts (37,38). However, no studies are available that compare the disease course of Dupuytren's disease following radiotherapy to the natural course of the disease, which would be important since it is not necessarily true that all patients with Dupuytren's disease have progression (39). Also, there are not enough data on long-term adverse effects, which is why it is not a widely used and accepted treatment modality. Slightly more is known about the use of pharmacological agents, aiming at control of the activity of myofibroblasts, which play a large role in the formation of contractures. Different agents have been described, such as anti-inflammatory drugs (i.e. steroids), anti-mitotic drugs (i.e. anti-tumor necrosis factor (TNF)) and hormonal therapy (i.e. tamoxifen). These agents were either applied topically, injected locally or administered systemically (40-43). Currently, the value of intra-nodular anti-TNF is further investigated, which may lead to regression of Dupuytren's disease, since TNF promotes the development of myofibroblasts (44). Unfortunately, no treatment is available yet for routine use, as there is no proof of short- or long-term success. However, with the on-going progress in the understanding and treatment of Dupuytren's disease, it is expected that a treatment that can control the disease will be developed in the near future.

Outcome measures for patients with early Dupuytren's disease

As mentioned previously, patients with Dupuytren's disease usually present at the hospital when they have established flexion contractures. The severity of contracture is most commonly determined by measuring the degrees of extension deficit per joint, using a goniometer (45,46). The extension deficit can either be measured actively or passively and when the deficits per joint are added up per finger, they form the total active or passive extension deficit. Both are used in the literature, but the TPED is more frequently used. Measurement of TPED is used to monitor disease severity and progression, but also to evaluate surgical treatment. However, it cannot be used for patients with early disease, as they do not have contractures yet. Not many researchers focus on this "subclinical" population primarily, because these patients generally do not experience many disease symptoms or are even unaware of having the disease and do not seek medical advice. This is probably why hardly any study has focused on the validation of reliable outcome measures for the measurement of disease extent in

patients with early disease. However, with the growing interest in therapies aiming at disease control in patients with early disease, there is need of objective and reliable outcome measures for this population. In one study on the agreement of several clinical outcome measures, the measurement of area of nodules and cords is described, using a tumorimeter (47). The authors found a high intra-observer agreement for all fingers except the right thumb (which was moderate). The inter-observer agreement was slightly lower overall and the middle-finger had a moderate agreement on both sides. They conclude that this newly introduced method can accurately measure disease extent in patients without contractures. Unfortunately, with this method only the projection of nodules and cords on the skin of a patient can be measured. It gives no information about depth, which is an important additional parameter as there is no evidence that Dupuytren's tissue expands equally in all directions. On the contrary, when Dupuytren's fibers contract, the area of its surface projection on the skin of the palm may decrease, while the disease does progress (figure 1).

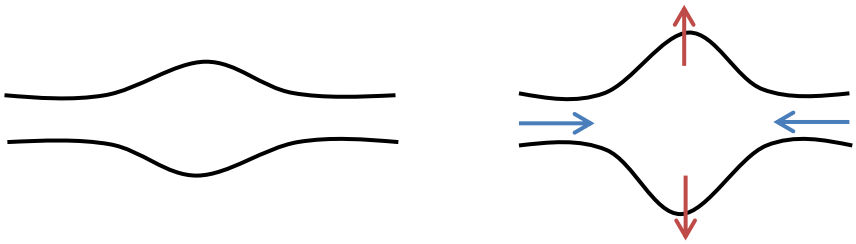

Figure 1. A nodule in a Dupuytren's cord in the sagittal plane. When the cord contracts (blue arrows), the thickness of the nodule may increase (red arrows).

Another possible outcome measure that may be used for patients with early Dupuytren's disease is the measurement of tissue hardness, using a tonometer. It is likely that hardness of Dupuytren's disease varies, depending on the histopathological stage it is in. Hereby, it may be possible to assess disease stage and maybe even predict progression of Dupuytren's disease. Previous research has shown that tonometry can distinguish Dupuytren's tissue from normal tissue and that the reliability of tonometry is excellent (48). However, no literature on nodule hardness and its possible relation with disease stage, is available yet.

Finally, studies on ultrasound (US) for Dupuytren's disease are expanding (49). It may be used to assess thickness of Dupuytren's tissue in the palmar to dorsal direction (depth), visualise the borders and possibly even to assess disease stage. Some studies also report the use of magnetic resonance imaging (MRI). Both US and MRI are non-invasive and do not have any deleterious effects (e.g., the radiation risk of computed tomography)(50,51). US

is the most patient-friendly technique and is also easier to access for clinicians. Currently, small, portable US machines are available, that can be used at the patient's bedside or at the outpatient clinic.

Ultrasound as new measurement tool for Dupuytren's disease

Previous studies have shown that Dupuytren's disease can best be visualised using a high-frequency probe (preferably 15-18 mHz) (52-55). The normal palmar aponeurosis appears as a thin echogenic lamellar structure overlying the flexor tendons. When affected by Dupuytren's disease, this layer becomes thickened and easier to observe (54). Dupuytren's nodules can be observed in two different planes (sagittal and transverse)(52). Also, US can assess the actual borders of a nodule, distinguishing it from the overlying skin (52,54). This all may lead to a more accurate measurement of nodule size, compared to measurement of nodule size with a tumorimeter, where the overlying skin is included in the measurement. Dupuytren's tissue has different types of echogenicity, which is the amount of ultrasound-waves that is reflected, when comparing it to the underlying flexor tendons. It has been suggested that echogenicity is related to activity of Dupuytren's nodules (54). Early stage nodules, which contain an abundance of myofibroblasts, are thought to appear as hypo-echogenic areas, which means that they are darker when comparing them to tendon (56). More advanced disease has a larger load of collagen fibers, and is thought to appear iso-echoic or hyper-echoic, which means that it has the same aspect as the tendons respectively, or even lighter (54,56). Finally, with US it is possible to assess changes in anatomy, and an altered course of the digital neurovascular bundles in particular (57,58). The presence of a spiral-, lateral- or abductor digiti minimi-Dupuytren's cord can lead to displacement of the neurovascular bundle (59). Transection of a digital nerve is a feared and unfortunate complication of open surgery for Dupuytren's disease, with a reported incidence of 1.9-7.8% (59). The risk decreases with minimally invasive surgery (1-4%), but is not zero (59). Pre-or peroperative US may be able to enhance safety of surgical procedures.

No studies have been conducted yet to assess the reliability of US for the measurement of nodule size and echogenicity of Dupuytren's disease. Also, the theory that echogenicity of Dupuytren's disease nodules is related to disease stage has never been substantiated by a histological study. Moreover, it is unclear whether the presence of hypo-echogenic areas has predictive value for progression and is therefore of clinical relevance. Finally, only a few small studies have been performed that assess the use of US to improve safety and efficacy of currently available treatment strategies in patients with Dupuytren's contractures (60,61).

Before US can be implemented in the standard monitoring and treatment of patients with early and more advanced stage Dupuytren's disease these topics have to be investigated more thoroughly.

Aims of thesis

With the ongoing developments in the field of Dupuytren research, it is likely that there is an interesting position for the use of US in the improvement and development of treatment strategies. The main objectives of this thesis are to systematically review the current knowledge on the use of US for Dupuytren's disease, to assess the reliability of this relatively newly introduced diagnostic device, to investigate its value for the assessment of disease activity and to evaluate the value of US when added to the regular work-up of patients undergoing treatment.

Outline of thesis

The use of US for patients with Dupuytren's disease is relatively new, but the amount of studies describing several purposes for this device is expanding. To get more insight in the possible applications for US and to address the topics that are in need of further research, a systematic review was conducted, which is presented in **Chapter 2**.

US can be used to measure several aspects of a Dupuytren's disease nodule, like size and echogenicity. Both aspects could be of relevance in monitoring the disease and treatment outcome in patients with early Dupuytren's disease. However, as it is a dynamic device, it is prone to all kinds of variety, like probe direction, amount of pressure and interpretation of US image. To assess the reliability and interpretability of the measurement of nodule size, the intra- and inter-observer reliability and the maximum dispersion of the measurement of nodule size was determined, by calculating measurement error and the smallest detectable change (**Chapter 3**). This was done so that in future studies we know which in- or decrease in nodule size can be called progression or regression beyond measurement error. In **Chapter 4**, the intra- and inter-observer reliability of subjectively rated echogenicity of Dupuytren's disease nodules was assessed.

In this **Chapter 4**, we also assessed the relation between echogenicity of nodules and disease stage, by following patients with early Dupuytren's disease for the period of one year, to see if echogenicity was predictive of growth of a nodule. This possible relation of echogenicity of Dupuytren's nodules and disease stage, was further explored in **Chapter 5**, in which the cords of patients undergoing limited fasciectomy were assessed with ultrasound prior to surgery and analysed for the amount of myofibroblasts by histopathological investigation after surgical removal.

In the last two chapters, the clinical relevance of US for Dupuytren's disease was investigated in two cohorts of patients undergoing minimally invasive surgery (PNF). **Chapter 6** focuses on the use of pre-operative ultrasound in order to enhance efficacy and safety of the PNF. In a similar cohort (**Chapter 7**), we aimed to show the relevance of being able to assess disease stage, by assessing if echogenicity of Dupuytren's cords is also related to disease progression, defined as time to recurrence following PNF.

The results of research described in this thesis are critically discussed in **Chapter 8**. Also, recommendations for future studies using ultrasound for patients with Dupuytren's disease are presented in that chapter.

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