Abstract Book

Friday, 22 May 2015

(including posters)
Lecture: Treatment of Dupuytren Disease in different countries and the role of FESSH and IFSSH in promoting knowledge for hand surgeons

Zsolt Szabo, Traumatology B.A.Z. Teaching Hospital, Miskolc, Hungary. President elect IFSSH
The epidemiology of surgical intervention for Dupuytren’s Contracture in England

Joseph Dias, ATOMS, University Hospitals of Leicester, LE5 5PW, UK.

We investigated the nationally collected data (Hospital Episode Statistics) to establish the variation in interventions for Dupuytren’s contracture.

We looked at data from the 143 NHS hospitals doing such surgery in England. The diagnosis was based on ICD-9 codes and the procedures were noted using OPCS-4.3 codes which are routinely used in the UK. Length of stay was available for each case. The population served by each hospital was derived from National datasets. Cost of treatment was calculated from the PbR Tariff of the NHS.

In England 16,068 patients had surgery for Dupuytren’s contracture in 2012 costing £53 million. Surgery excises or divides the cord causing finger contracture and this is the standard established treatment. If this is extrapolated to the 28 European Union countries in 2014 with a population of 507,416,607 we would have 152,414 cases needing treatment for Dupuytren’s contracture and if the costs were similar to those in the UK, the annual cost of treatment for Dupuytren’s contracture in Europe would be €642 million.

Only 7% had fasciotomy with 45% having palmar surgery and 37% having digital surgery. Revision surgery accounted for only 2.8% of our cases. Not only is the type of surgery done (see figure) and the rate different between hospitals but the way patients are treated also differs. The figure shows the funnel plot of Dupuytren’s contracture cases treated as day cases in this year in the United Kingdom. There is huge variation in the rate of surgery, the treatment choice and the LoS in England.
Favorite Options of German Hand Surgeons in the Treatment of Dupuytren’s Disease

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Hypothesis: It has been said that in Germany needle aponeurotomy (NA) is standard of choice in the treatment of Tubiana stage I and II in Dupuytren’s disease.

Method: Using a web-based questionnaire the members of the German Society for Surgery of the Hand are being invited to declare, which treatment option they prefer, in relation to Tubiana stages I to IV.

Results: The study is not closed yet. Preliminary results show that NA is not favored by the majority of hand surgeons. They prefer to perform open surgery, especially in significant flexion deformity. In early stages many surgeons recommend to wait until the deformity has worsened. Statistical analysis will include descriptive and correlation tests.

Summary: It can be expected that this survey shows that in Germany the vast majority of hand surgeons offer traditional surgery alone. NA is being practiced only sporadically, enzyme fasciolysis even more rarely.
Trends in Dupuytren’s Treatment in the United States

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Hypothesis: The treatment of patients with Dupuytren’s contracture has changed significantly over the past decade in the United States (US) since the Federal Drug Administration (FDA) approved the use of clostridium collagenase histolyticum (CCH) in February 2010. We hypothesize that the introduction of CCH for the treatment of US patients with Dupuytren’s contracture will be associated with an increase in the incidence of Dupuytren diagnosis made and a decrease in the distribution of open surgical interventions.

Methods: The IMS Health Hospital Procedure/Diagnosis database was analyzed from January 2007 through December 2013 for the diagnoses (ICD 718.44, 728.6) and surgical procedure codes for open surgery (Fasciectomy or Fasciotomy, CPT 26121, 26123, 26125) versus needle aponeurotomy (NA, CPT 26040, 26045). CCH usage trends data were derived from the Auxilium CCH data warehouse starting from February 2010. CCH procedure frequency was calculated based on actual vial sales divided by 1.1 vials per procedure (based on a recent clinical effectiveness study); this was done in order to translate CCH vial sales into the same/similar units as surgery and NA. Quarterly procedure trends were analyzed before and after the introduction of CCH to the market.

Results: The average monthly Dupuytren’s ICD codes reported increased 69% from January 2007 (13,000) to December 2013 (22,000). The average quarterly number of total surgical procedures decreased 18.7% from 11,718 in 2007-2009 to 9,869 from 2011-2013. Since the approval of CCH in Q1 2010, the use of CCH has steadily increased from 5% of all discharged procedures to 20-30% in 2013. This coincides with a decrease in the percentage of surgical procedures from 80% of total CPT codes to only 60%. The percentage of NA remained relatively steady at approximately 10% throughout the study period. The surgical treatment of Dupuytren’s contracture was found to be seasonal with more significantly more surgeries performed in the months of January, February and March.

Summary:
- The diagnosis of Dupuytren’s contracture has increased significantly with the introduction of CCH in 2007.
- The increase in CCH use correlates with the decrease in open surgery.
- The percentage of NA procedures remained unchanged during the same time period.
- A seasonal variation in surgical treatment for Dupuytren’s contractures was documented with significantly more procedures in the winter months.
Hypothesis: Potentially there might be a discrepancy between the actual expectations and views of patients and what their doctors believe to be their patients’ view. An overall overview of preferences and guidelines for individual assessment are required.

Method: To get a better understanding how patients view their treatment options and what their preferences are, an international survey of patients suffering from Dupuytren and/or Ledderhose disease was conducted. Patients were recruited from Dupuytren forums of the International Dupuytren Society, the British Ledderhose Disease Blog, the German Dupuytren-Gesellschaft (using an equivalent German questionnaire and providing an example of country specific responses), the US Dupuytren Foundation, and from a British survey of patients having had fasciectomy.

The survey was conducted using an online questionnaire and, for the British fasciectomy patients, an interview. Patients were free to fill out the whole questionnaire or parts of it. The questionnaire addressed both, Dupuytren and Ledderhose disease.

Results: The survey is still ongoing. So far well over 2,000 patients have responded. The response rate is about 25 %. Participants were predominantly from the USA, the UK, and Germany.

This paper addresses responses regarding Dupuytren disease. Ledderhose results are presented in a separate paper. Preliminary results show considerable differences in the assessments of treatment options, including a preference for minimal invasive treatments, irrespective of faster recurrence. For limited fasciectomy a relatively high percentage (> 10%) reported that the surgery “made it worse”, as compared to about 1 % for PNF or radiotherapy. Patients drinking more than 2 glasses of alcoholic drinks per day are on an average reporting an earlier onset of the disease by 2+ years, smokers an earlier onset by 6 years.

Summary: Results show a preference for minimal invasive treatment but for progressed states fasciectomy is experienced as equally effective. A fairly large spread of ratings for all treatments emphasizes the requirement to assess individual needs and expectations before deciding for a specific treatment.
Patients’ preferences for treatment for Dupuytren’s disease: a Discrete Choice Experiment


Hypothesis: Many treatment options are available for Dupuytren’s disease (DD) and these treatments differ significantly in attributes such as amount contracture correction, complication rate, convalescence, and time to recurrence. Since not all treatments are equally successful in optimizing all these attributes, it is important to understand patients’ preferences. For example: how much change of recurrence is a patient willing to trade for an earlier return to work. Therefore, the aim of this study is to determine patients’ preferences for different techniques of Dupuytren treatment and their attributes by using a discrete choice experiment.

Methods: We approached 973 patients who had undergone a treatment for Dupuytren’s disease between January 2009 and August 2012 to evaluate their choice of treatment. These patients were asked to fill in a questionnaire in which they had to repeatedly choose between different three hypothetical treatments. Each hypothetical treatment was characterized by different levels (values) of 7 different attributes: (1) Treatment method, (2) major complications rate, (3) minor complications rate, (4) recovery period, (5) recurrence within 5 years, (6) extension deficit after treatment, and (7) aesthetic result. We analyzed the relative importance of these attributes and the trade-offs that patients were willing to make with a latent class model.

Results: The total response rate was 73%, of whom 506 patients filled in the complete questionnaire. We found that the levels of all 7 treatment-attributes significantly contributed to the final treatment choice. Post treatment extension deficit and recurrence rate most significantly contributed to treatment choice, whereas aesthetic result and recovery time seemed less important. We also calculated the trade-offs patients were willing to make for ‘recurrence of disease’ and ‘contracture correction’. Patients accepted an increase of 10.5% recurrent disease if they could receive needle aponeurotomy treatment instead of limited fasciectomy. Furthermore, patients accepted a 10% increment of recurrent disease for every 5% reduction of major complication. For a decrement of 8.5% of the post intervention contracture correction patients accepted a 5% reduction in major complication rate and for every 9% decrement in reduction of the post intervention contracture correction they accepted 10% reduction of recurrence rate.

Summary: In this discrete choice experiment, we were able to calculate the trade-offs patients were willing to make for ‘recurrence of disease’ and ‘contracture correction’. We showed that patients are willing to receive a treatment with a higher change of recurrence of DD if the chance of major complications was smaller. Also, patients considered post treatment contracture reduction more important than recurrent disease rate. This study gives us more inside information what factors of treatment for DD patients find important, which may improve treatment selection during the patient-doctor interaction.
Lecture: The extra-cellular matrix in Dupuytren’s disease

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The maintenance of normal tissue homeostasis relies on interactions between cells and their extra-cellular matrix, a concept described originally by Bissell in the 1980s as “dynamic reciprocity”. Disruption of this reciprocity has been proposed to be causative and essential for the development of malignant diseases. The central hypothesis of this presentation is that the dynamic reciprocity concept can be extended to enhance our understanding of Dupuytren’s disease (DD) progression, recurrence and treatment. This presentation will provide an overview of the extra-cellular matrix in DD, its characteristics and roles in regulating DD development and recurrence. The importance of taking the modifying effects of extra-cellular matrix constituents and biomechanics into account when assessing potential molecular targets to treat DD will be illustrated in the context of matrix-induced changes beta catenin levels. Beta catenin is a central and essential component of the canonical Wnt signaling pathway, a pathway that has become a major focus for understanding DD development and for identifying molecular targets as novel therapies for DD. In addition to matrix-induced changes in beta catenin levels, the effects of minor changes in extra-cellular matrix tension on the gene expression of DD myofibroblasts will be illustrated and discussed. Finally, the potential to expand on current therapies that specifically target the extra-cellular matrix in DD, such as collagenase injections, will be addressed in the context of developing new, multi-focal approaches to preventing DD progression and recurrence.
Hypothesis: Dupuytren’s disease (DD) is a fibro-proliferative disease of the palm of the hand that results in contracture of the fingers. Myofibroblasts, which are the cells responsible for contraction, extracellular matrix (ECM) production and remodeling are thought to be the driving force for this disease. We hypothesize that by targeting the activated myofibroblast we will be able to reduce the fibrotic load in DD affected tissue.

Method: We previously have generated an ex vivo culture system in which we can maintain the tissue in its original three-dimensional (3D) structure. We focus on the molecular pathway of interferon gamma (INF-γ), a cytokine with immunomodulatory and anti-fibrotic effects. Intratreatment injections of INF-γ have been shown to exert a beneficial effect on the disease by decreasing the symptoms and size of the lesions. However, due to the ubiquitous expression of its receptor, myofibroblast-specific targeting is challenging. DD myofibroblasts express, as in most fibrotic tissue, high levels of platelet-derived growth factor receptor-beta (PDGFR-β) in comparison to healthy tissue. We have investigated a targeting approach using BOT191, a synthetic polypeptide in which the signaling domain of INF-γ is conjugated via a 2kDa PEG linker to a bicyclic peptide, that binds specifically the PDGFR-β and not the INF-γ receptor. BOT191 lacks the IFN-γ receptor binding domain therefore does not activate macrophages and other immune cells.

Results: Administration of this compound to DD tissue in our ex vivo setting has shown a dose-dependent reduction of the ECM proteins associated with fibrosis. In particular, we have observed at various time points (e.g. day 3 and day 7 after ex vivo culture) reduction in alpha smooth muscle actin, collagen type I and type III expression. In addition, both proliferation and apoptosis have not been affected by the administration of the BOT191. The composition of immune cells in the fibrotic parts and the potential effect of the BOT191 compound are also characterized in our 3D model. Our data indicate that activated mast cells are present in Dupuytren’s fibrosis and possibly contribute to myofibroblast phenotype by enzymatic remodeling of ECM and increased availability of profibrotic cytokines.

Summary: The therapeutic state of the art for DD is surgical removal of the fibrotic tissue. The recurrence rate is high necessitating more surgeries. In this study we assessed the effect on the fibrotic load of BOT191. Specific targeting of myofibroblasts and modulation of the interplay between immune cells and (myo)fibroblasts might lead to improved anti-fibrotic approaches. We conclude that BOT19:

- Reduces alpha Smooth Muscle Actin, Collagen Type1 and Type3
- Has no effect on proliferation and apoptosis
**Wnt pathway in Dupuytren disease, connecting pro-fibrotic signals**

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**Hypothesis:** Wnt signaling is known to be pro-fibrotic, however, no complete overview exists of the changes in this pathway during Dupuytren disease. We propose that Wnt signaling plays an important role in Dupuytren disease and present here a comprehensive overview of changes in Wnt signaling in Dupuytren tissue compared to normal fascia.

**Method:** We performed a Wnt pathway array on nodules and unaffected transverse ligaments of the palmar aponeurosis (TLPA) of 12 Dupuytren patients, and found significant changes in 41 out of 102 Wnt-related genes, as analyzed by Wilcoxon paired rank test. Selected parameters from the array were explored further using immunohistochemistry onDupuytren and control tissue to investigate protein expression. Mechanistical function of several changed genes was examined using in vitro experiments on primary fibroblasts isolated from nodules and on non-diseased fibroblasts.

**Results:** Out of 12 genes coding for Wnt proteins, 5 were downregulated and 1 was upregulated in nodules compared to TLPA. Canonical Wnt targets FOSL1, LEF1 and WISP1 were significantly upregulated; 6.6, 4.6 and 2.9× respectively. Immunohistochemistry revealed a 25-fold increase of the pro-fibrotic WISP1 protein in nodules. However, knockdown of WISP1 using siRNA in primary Dupuytren’s fibroblasts did not reduce fibrotic parameters. Other highly upregulated genes were components of the non-canonical Wnt pathway, WNT5A, NKD1, PRICKLE1 and VANGL2. The increase in non-canonical Wnt signaling was also confirmed at the protein level, along with increased expression of non-canonical co-receptors Ror2 and Ryk. Strikingly, the strongest downregulated genes in this study were four antagonists of Wnt signaling; DKK1, FRZB, SFRP1 and WIFI (0.100, 0.113, 0.134 and 0.021 × control values respectively). The downregulation of these genes in patient tissue could be mimicked in vitro by treating non-diseased fibroblasts with TGF-β1, suggesting crosstalk between the different pro-fibrotic pathways. Furthermore, siRNA mediated knockdown of all four antagonists in non-diseased fibroblasts led to an increased nuclear staining for canonical Wnt mediator β-catenin in response to TGF-β1 treatment.

**Summary:**

- Extensive dysregulation of Wnt signaling exists in tissue from Dupuytren patients compared to patient-matched TLPA.
- The changes found suggest that both canonical and non-canonical Wnt signaling are upregulated in Dupuytren disease.
- The upregulation may be partly due to a downregulation in endogenous antagonists of Wnt signaling, which can in its turn be linked to other pro-fibrotic signaling pathways, such as the TGF-β pathway.
Biomarkers of post-surgical outcome in Dupuytren’s disease

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Hypothesis: The measurement of circulating proteins of the matrix metalloproteinase (MMP) or tissue inhibitors of metalloproteinases (TIMP) families will be predictive of post-surgical outcome after fasciectomy for Dupuytren’s disease (DD) measured through Total Extension Deficit (TED). This is true for the expression of genes in tissues taken at surgery (Johnston et al. 2008).

Methods: Surgery was performed at the Norfolk & Norwich University Hospital with ethical approval and all patients provided informed consent. Tissue from patients with DD was taken at fasciectomy (n=25, age range 44-78 years, 5 women, 20 men). Normal palmar fascia was taken from patients without clinical DD who had carpal tunnel release (n=30, age range 37-86 years, 20 women, 10 men). Blood was taken for plasma into sodium citrate pre-surgery. RNA was extracted and gene expression measured by quantitative RT-PCR or Illumina Human HT-12 v4 Expression BeadChip (Source Bioscience UK). Protein measurement was by ELISA. Preoperative and early (mean=44 days) post-operative scores were obtained for total extension deficit using a digital goniometer measuring active extension. Grip strength was measured with a hydraulic hand dynamometer.

Results: The study thus far has assayed correlations only with pre-surgical and early post-surgical measurements. MMP-1, MMP-2, MMP-3, MMP13, MMP-14 and TIMP-1 were assayed in plasma and their levels correlated with clinical measurements. Only circulating MMP-14 levels correlated with pre-surgical and early post-surgical total extension deficit (TED). In order to extend this study, we measured the whole genome transcriptome in tissue samples from ten DD patients and examined correlation to pre- and early post-operative TED. Interestingly, the expression of >100 genes correlated with these measures with high correlation coefficient (R>0.8 or R<-0.8).

Summary: These results show correlation between a circulating protein and preoperative or early post-operative clinical measurements. Whilst this will not change surgical practice, it demonstrates the utility of the approach and raises the possibility of predicting surgical outcome. We will perform similar measures of TED and patient-reported outcome measures at approximately one year follow up to determine the predictive nature of any of the protein or gene expression measurements taken.

“Metalloproteinase gene expression correlates with clinical outcome in Dupuytren’s disease”
Hypothesis: Myofibroblasts, the cells responsible for matrix production and contraction in Dupuytren’s disease (DD), develop as a result of local production of cytokines and coordinate their activities to function as a syncytium.

Methods: We characterised the cells present in Dupuytren’s nodules. Cytokines produced by freshly disaggregated cells from DD nodules were measured by electrochemiluminescence. Next, we compared the effects of these cytokines on contraction and pro-fibrotic signaling pathways in fibroblasts from the palmar and non-palmar dermis of Dupuytren’s patients, and palmar fibroblasts from normal individuals. We then determined the effect on the myofibroblasts phenotype of inhibition of these cytokines. The effect of inhibition of adherens, mechanosensitive or gap junctions on the contractility of myofibroblasts in 3D collagen gels in a culture force monitor was also assessed.

Results: Together with the myofibroblasts, we found significant numbers of immune cells, including classically activated macrophages in the nodules. High levels of pro-inflammatory cytokines were detected in tissue from Dupuytren’s patients. Exogenous addition of TNF, but not other cytokines, including IL-6 and IL-1β, promoted differentiation into specifically of palmar dermal fibroblasts from Dupuytren’s patients in to myofibroblasts. We also demonstrated that TNF acts via the Wnt signaling pathway to drive contraction and pro-fibrotic signaling in these cells. We examined the effects of targeted cytokine inhibition. Neutralizing antibodies to TNF inhibited the contractile activity of myofibroblasts derived from Dupuytren’s patients, reduced their expression of α-smooth muscle actin, and mediated disassembly of the contractile apparatus. Four of the anti-TNF agents approved for clinical use are administered subcutaneously. We found that all were effective in reducing the contractility of myofibroblasts in vitro.

Summary: Our data indicate that myofibroblasts function as a coordinated cellular syncytium(1). We have also shown that localized inflammation in Dupuytren’s disease contributes to the development and progression of this fibroproliferative disorder and identified TNF as a therapeutic target to down regulate myofibroblast differentiation and activity(2). We are now proceeding to phase I and II clinical trials using anti-TNF for patients with early DD.
Controversies 1:

Pathogenesis of Dupuytren Disease: active or passive contracture?

Chair: David O’Gorman

Active contracture proposed by Jagdeep Nanchahal

Passive contracture proposed by Charles Eaton
Friday, 22 May 2015, 13:00

Lecture: Genetics in Dupuytren Disease

Roel Ophoff, David Geffen School of Medicine, UCLA, Los Angeles, USA.
A Large European Genome-wide Association Study Reveals Multiple New Genetic Susceptibility Variants for Dupuytren’s Disease

Michael Ng, Southam, Hennies, Werker, Izadi, Espirito-Santo, Thakkar, Nanchahal, Zeggini, Furniss, NDORMS, Oxford University, Windmill Road, Oxford, OX3 7LD, UK; Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire CB10 1SA, UK; Universität zu Köln, Cologne Center for Genomics, Weyertal 115b, 50931 Köln, Germany; University Medical Centre Groningen, Hanzeplein 1, BB81, 9700 RB Groningen, The Netherlands.

Hypothesis: Dupuytren’s disease (DD) is a common condition, which predominantly affects people of Northern European origin. In addition to the genetic predisposition, risk factors including diabetes, hypercholesterolemia and smoking, making DD a typical complex disease. Previous work from our collaboration has implicated nine variants in the genetic predisposition to DD. We hypothesised that by increasing the number of cases and controls in our genetic analysis, we would discover additional variants predisposing to DD. Our aim was to acquire a better understanding of the genetic predisposition to the disease and the dysregulation of the underlying molecular mechanisms and pathways, in order to develop novel therapeutic strategies.

Materials and Methods: As part of the BSSH Genetics of Dupuytren’s Disease collaboration, we performed a Genome Wide Association study (GWAS) utilising a UK case-control cohort consisting of 9,115 individuals. Replication analysis was undertaken using samples from both Germany (German Dupuytren Study Group) and Holland (Dutch Dupuytren Study Group). The UK discovery cohort was genotyped on the Illumina CoreExome DNA microarray to assess the variants at 538,448 positions across the whole human genome. Replication analysis was conducted on other platforms, including Sequenom MassArray and Taqman. For immunocytochemistry and gene expression assays, we used myofibroblasts cells derived from patients who underwent fasciectomy.

Results: We replicated association at eight of nine previously described variants. In addition, we discovered four new regions – on chromosome 6 (near SUMO4); on chromosome 8 (near EBF2); and two on chromosome 14 (in MMP14, and near ATL1) - associated at genome-wide significance (p<5.0 x 10^-8). Preliminary expression experiments suggest that the genotype at the most highly associated variant (rs16879765, p=5.18 x 10^-41) alters the expression of SFRP4 in myofibroblasts, identifying a potential therapeutic target.

Summary: Our results have provided further insights into the molecular mechanisms crucial for the development of DD. This information will be used in the future to develop novel therapeutic strategies aimed at preventing primary disease or recurrence after intervention. Further imputation and functional analyses are ongoing.
Hypothesis: Dupuytren’s disease is a complex disease with a strong genetic basis. To unravel this genetic basis we performed a genome-wide association study (GWAS) comparing cases and controls for single nucleotide polymorphisms (SNPs) to identify genomic regions that are associated with the disease.

Methods: We included 1,580 cases and 4,491 controls in a meta-analysis of three genome-wide imputed GWAS datasets. Using linkage information from large reference cohorts (1000 Genomes or HapMap) allows the imputation of many more SNPs than were genotyped on the array.

1. Dataset: 186 cases and 447 controls (KORA, Helmholtz Center Munich) genotyped for 904440 SNPs on the Affymetrix Genome-Wide Human SNP Array 6.0
2. Dataset: 538 cases and 1208 controls (Popgen, University of Kiel) genotyped for 587352 markers on the Affymetrix Axiom Genome-Wide CEU 1 Array
3. Replication dataset: 856 cases (Dr. G. Dolmans, Prof. P. Werker, Prof. C. Wijmenga and coworkers, University Medical Center Groningen) and 2836 controls (LifeLines) genotyped for 234939 markers on the Illumina HumanCytoSNP-12

After quality control each GWAS dataset was imputed with IMPUTE2 and the EUR 1000 Genome reference set. For the meta-analysis we used a fixed effects model adjusting for population stratification.

Results: Our preliminary data set confirms all previously identified GWAS loci, 7 of 9 with significant findings. Moreover, it points to further loci associated with Dupuytren’s disease with genome-wide significance. Our biostatistic data analysis will be finished in January 2015.

Summary:
- Genome-wide imputation increases the association power for finding new risk loci in Dupuytren’s disease.
- Previously identified susceptibility loci for Dupuytren’s disease can be replicated and further loci exist.
- Sequencing of the GWAS loci is the next step to identify underlying causative genetic variant
Identification and characterization of functional genetic variants in Dupuytren’s Disease

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Hypothesis: Dupuytren’s Disease (DD) is a complex disorder, which results from interactions of individual genetic predisposition and multiple environmental influences. We aim to identify causative variants, including both coding and noncoding variants, which directly predispose to DD.

Method: We have previously identified disease-associated chromosomal regions using genome-wide association studies (GWAS). Validated GWAS-identified candidate regions are being further analyzed for variants that could explain the disease-association signals using targeted next-generation genomic sequencing. The function of these variants for gene expression, myofibroblast functional properties and regulatory pathways involved in DD pathogenesis are being tested in patient RNA and fibroblast samples from disease tissues.

Results: We have identified coding and noncoding variants for the first time to our knowledge, potentially functional variants in GWAS-associated regions in DD patients. Coding variants were validated in additional patients by Sanger sequencing. Noncoding variants are analyzed for expression quantitative trait loci (eQTLs) and possible regulatory effects.

Summary:
- Potentially causative coding and noncoding variants are identified in DD patients
- This study may lead to a better understanding of the etiology and pathogenesis of DD
- The identification of potentially causative variants may provide a future opportunity to identify new targets for treatment of DD
A systematic review and meta-analysis on the association between Dupuytren disease and diabetes


Introduction: The precise etiology of Dupuytren disease (DD) remains largely unknown. In addition to genetic factors, environmental factors are often associated with DD. Beside, DD has frequently been associated with other diseases, such as diabetes. However, the different studies reporting an association between DD and diabetes have conflicting results. Therefore, the aim of this study was to examine the strength and consistency of the relationship between Dupuytren disease and diabetes in published studies reporting an association between the two conditions.

Method: MEDLINE, EMBASE and Web of Science databases were searched for articles reporting an association between DD and diabetes published before June 17th, 2014. The frequency of both DD and diabetes were extracted from the articles, as well as information on age and diabetes type. Random effects meta-analysis was performed to quantify the association between DD and diabetes. Additionally, the association between DD and diabetes was corrected for age differences between studies, using a generalized linear mixed model.

Results: The search yielded 1308 articles. Of these, 32 articles were included, investigating 24,553 patients. A significant association between DD and diabetes was observed (OR = 3.4; 95% CI 2.7 – 4.2). After correction for age using a generalize linear mixed model, this association remained significant. The presence of Funnel plot asymmetry suggests that there is publication bias. Indeed, small studies reported larger OR’s compared with large studies.

Conclusions: This is the first study that quantified the association between DD and diabetes using meta-analyses. The findings demonstrate a significant and consistent association between DD and diabetes. Diabetes is a risk factor that should be addressed when conducting research investigating participants with DD. Prospective, longitudinal studies are needed to elucidate the pathways causing this association.
The association between vibration and Dupuytren disease: a comparison between elderly field hockey players and controls

Dieuwke Broekstra, Inge Smits, Tom Harder, Edwin R. van den Heuvel, Paul M. N. Werker, University Medical Center Groningen, Department of Plastic Surgery, Hanzeplein 1, 9700 RG Groningen, The Netherlands.

Introduction: Dupuytren disease (DD) is a fibroproliferative condition involving the palmar fascia of the hand. The etiology remains largely unknown, and the role of exposure to vibration as risk factor has been studied with contradicting results. The hypothesis of the current study was that vibration is associated with DD in elderly field hockey players.

Methods: In this cross-sectional study, the hands of 174 elderly male field hockey players and 152 male controls were examined for signs of DD. Details about the participants' age, lifestyle factors, medical history, employment history and leisure activities were gathered during an interview. The association between vibration exposure and DD was determined using multivariable logistic regression analyses.

Results: DD was found in 48.3% of the field hockey players, and in 25.0% of the controls. Multivariable logistic regression analysis showed that age and vibration as dichotomous variable, were significantly associated with DD. To test whether there was a dose-response relation, a multivariable logistic regression analysis within the group field hockey players was conducted, using vibration as continuous outcome (hours/week * years). Using this model, only age was significantly associated with DD.

Discussion/Summary: In this sample, exposure to vibration was associated with DD. However, a dose-response relation could not be found. As the power in this study was sufficient, the results suggest that the intensity and duration of the vibration is not an important risk factor for DD. It might be that other factors, such as recovery time or vibration frequency, play a larger role.
Controversies 2:

The benefit of splinting for Dupuytren Contracture

Chair: Ilse Degreef

Splinting confers no benefit: Adrian Chojnowski

Splinting is beneficial: Wolfgang Wach
Friday, 22 May 2015, 15:15

**Lecture: Collagenase Treatment – Journey from Bench to Current Advanced Clinical Use**

**Larry Hurst**, Stony Brook University Medical Center, NY, USA, 11794

The history of the collagenase development for the treatment Dupuytren's disease at the University at Stony Brook is presented. The story begins even before our invention of the Collagenase Treatment for Dupuytren's Contracture with others who discovered and isolated collagenase. We began the development of collagenase at Stony Brook in 1991, when Advanced Biofractures Corporation of Long Island (now BTC) brought collagenase to the attention of our research team. BTC had licensed collagenase for the treatment of burns. They initially asked us if we would investigate its use in conjunction with nerve repair but we convinced them that a far better use would be treating Dupuytren's Disease. Dr. Badalamente and Hurst had been doing research related to Dupuytren's Disease since the early 1980s. Our preliminary collagenase studies were done in ‘91 and ‘92 with subsequent publications in Drug Delivery and the Journal of Hand Surgery. The investigational new drug number (IND) was obtained by the University at Stony Brook in 1994. Dr. Badalamente and Hurst obtained FDA orphaned drug status for collagenase in 1997. A patent was filed by BTC for the use of collagenase for the treatment of Dupuytren's Disease in 1996. The Phase I and Phase II FDA approved research studies were then completed. The pivotal Phase III trial was began in 2007. This study, The Collagenase Option for the Reduction of the Dupuytren's disease (CORD study) Phase III trial was done in 16 sites in the United States and 5 sites in Australia. This study was conducted on 1082 patient who received 2630 injections. This CORD study was completed in 2009. At that time Auxilium Pharmaceuticals, Inc. licensed the technology from the BTC and obtained the IND from the University at Stony Brook. A revised US patent was granted in 2007. This study completed the Phase I, II and III trials requirements for the FDA and was the basis along with the prior studies for the New Drug Approval application presented to the FDA. The CORD study was published in a landmark article in the New England Journal of Medicine in September 2009. In 2009 United States FDA advisory committee voted 12 to 0 in favor of recommending the approval of collagenase for the treatment of Dupuytren's disease. In 2009 the American Orthopedic Research Society and the American Academy of Orthopedic Surgeons awarded the annual clinical researcher ward for the developmental collagenase to the Stony Brook team. In February 2010 United States FDA granted approval for the use of collagenase for the treatment of the patients with Dupuytren’s contracture in the United States. In April 2010 Dr. Badalamente and Hurst hosted the Dupuytren’s Disease Symposium at Stony Brook. Next insurance coverage issues in the United States were resolved and in the fall of 2010 Dr. Hurst began treating the 852 patients with Dupuytren’s contracture at Stony Brook who were waiting for the approval of COLLAGENASE (CCH). Since 2010, Dr. Hurst has treated 955 with Dupuytren’s Disease. Those patients with palmar nodules only [467 (49%)] have been treated with observation alone while those patients with Dupuytren’s cords [ 443 (46%) ] have been treated with COLLAGENASE (CCH). In addition patients with cords and special circumstances like deficit scarred skin after surgical recurrence or nodules associated with trigger fingers [ 45 (5%) ] have been treated with open surgery. In the research studies Dr. Hurst treated 257 patients with CCH. Since 2010 Dr. Hurst has done 611 clinical injections in 443 patients. Twenty patients have received double doses concurrently. Therefore my total number of Dupuytren patients (research + clinical) treated with CCH is 700.

The total number of treated clinical patients (CCH + surgery) since 2010 was 488.

**Session 7: Related Diseases & Other Treatments**
Since 2010 a Four Step extension procedure (manipulation procedure) has been developed and these procedures are done with buffered lidocaine local field blocks. The CCH injection treatment has also been extended to allow the successful treatment of many Dupuytren cord types and cord combinations with a single dose. Cord types that have treated included: Central cords causing isolated MP FC, Central cords causing isolated PIP FC, Central cords causing Combined MP & PIP FC’s, Abductor Digiti Minimi (ADM) cords, “Y” Cords (Combined Central & Natatory), “Crow Foot” Cords (Central cord and Two Natatory Cords causing 3 adjacent MP FC’s, “Super Y” Cords (Central Palmar Cord over 4th Ray with Natatory Cords to III & IVth fingers. Thin cords in adjacent fingers have also been successfully treated with a split single dose. Commissural Cords causing First Web contracture and Thumb Radial Cords causing Adduction contractures have also been treated. In addition lateral cords causing DIP contractures have been routinely treated successfully with CCH. It should be noted that in the US and Europe treating the thumb and DIP joints are “off label” use. Also using CCH without stopping anticoagulants has been carried out successfully but this has not been documented by prospective studies. A study of the efficacy of treating Dupuytren’s nodules is also nearing completion. Currently the CCH injection treatment has been further advanced by a research studies investigating the efficacy of using two doses of CCH at the same time in a hand with multiple cords and by studying the timing of the finger extension procedure at 24, 48 and 72 hours. The major two concurrent two dose study is entitled: Prospective Multicenter, Multinational Study to Evaluate the Safety and Efficacy of Concurrent Collagenase Clostridium Histolyticum Injections to Concurrently Treat Two Dupuytren’s Contractures in the Same Hand. This study used two doses of CCH in 2 joints in the same hand at the same time after injection. 714 patients representing 724 joint pairs involving 1448 joints (896 MP and 552 PIP joints) were studied. The majority of patients were very satisfied or quite satisfied. The results and side effects were very similar to the CORD studies. 64.6% of the MP joints and 28.6% of the PIP joints achieved a fixed flexion contracture (FFC) of less than or equal to 5 degrees. 89.3% of the MP joints and 71.6% of the PIP joints achieved greater than or equal to a 50% correction in their contracture. This study also showed the extension procedure could be done with equal results at 24, 48 and 72 hours after injection.
Dupuytren’s Disease in the thumb and first webspace and collagenase treatment

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Hypothesis: Treating contractures in the thumb and first web space of subjects suffering of Dupuytren’s Disease leads to an improvement in extension deficit and range of motion.

Methods: We designed a prospective cohort study and included twelve subjects. Fourteen thumbs were affected by Dupuytren’s Disease and had a contracture at the MCP joint of at least 20° with a palpable cord in the thumb, or an adduction contracture of the thumb with palpable cords in the first webspace. The subjects received an injection with 0.58 mg of CCH (Xiapex®) in the fibrous cord, divided over three spots. About 24 hours later manipulation and rupture of the cord was performed under local anesthesia. The extension and IMD were measured pre- and post intervention. Follow-up measurements took place at 7 and 30 days and 6 months post intervention.

Results: The measurements at 30 days and 6 months showed that all post intervention extension deficits were significantly lower than pre intervention (p<0.05). Similar results were found after analyses of IMD, however only in the last measurement 6 months post intervention.

In an analysis of subgroups the separate contribution of treatment of a pretendinous cord and a first web cord on both extension deficit and IMD were compared.

Injections in a pretendinous cord of the thumb resulted in significant improvement (p < 0.05) of all total extension deficit comparisons and almost all IMD comparisons. Interestingly however there were no significant effects on extension deficits found following first web cord treatment.

Summary:

- After treatment extension deficits were significantly lower in the total sample.
- Compared with pre injection, IMD was significantly improved after six months.
- No signs of recurrence were found during the 6 months follow up period.
- Injection in a pretendinous cord (n=8) showed significant improvement on both extension deficit and IMD.
- However there was no significant effect after treatment of the first webspace in our small sample (n = 6).
- We conclude therefore that in thumbs affected with Dupuytren’s Disease CCH is an effective treatment for pretendinous cords.
- Concerning CCH treatment in the first webspace we however conclude that further study is required.
Efficacy of using local anesthesia before collagenase injection in reducing overall pain experience in patients treated for Dupuytren’s contracture: A quasi-randomized study

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Hypothesis: Collagenase injection is increasingly used as a non-surgical treatment for patients with Dupuytren’s contracture. Currently, the standard practice is to inject the collagenase into the cords without prior local anesthesia. We observed, however, that many patients seemed to experience substantial pain during the collagenase injection. The hypothesis of our study was that injecting a local anesthetic before collagenase injection can reduce the patients’ overall pain experience during treatment.

Methods: Consecutive patients with Dupuytren’s contracture scheduled for collagenase injection were quasi-randomized into two groups: one received local anesthesia, as a nerve block in the proximal palm, approximately 20 minutes before collagenase injection (LA group), and the other received the collagenase injection without anesthesia (no-LA group). After reconstituting CCH with 0.39 ml of diluent all content that could be withdrawn into the syringe (approximately 0.80 mg) was injected into multiple spots in the cord. The anesthetic used was 10 mg/ml mepivacaine, buffered by diluting each 20 ml with 5 ml 50 mg/ml sodium bicarbonate. Immediately after receiving local anesthesia and/or collagenase injection the patients were asked by the nurse, independently of the treating surgeon, to rate the severity of the pain they experienced during the injection on a visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain). When the patients returned to the outpatient clinic for finger extension 1 or 2 days after the collagenase injection the nurse asked them to rate, on the same VAS scale, the severity of pain they had experienced during the time since they received the injection.

Results: The LA group included 83 patients (65 men), mean age 69 (SD 9) years, and the no-LA group included 78 patients (65 men), mean age 70 (SD 8) years. The mean score for pain experienced during the first injection (buffered mepivacaine in the LA group and collagenase in the no-LA group) was 2.3 (SD 1.7) for the LA group and 4.3 (SD 2.5) for the no-LA group; the age and sex-adjusted mean difference in pain score was -2.1 (95% confidence interval -2.7 to -1.5, p<0.001). In the LA group, the mean score for pain experienced during collagenase injection was 0.9 (SD 1.0). The mean score for pain experienced during the 1 or 2 days interval between injection and finger extension was similar in the two groups; 2.9 (SD 2.3) for the LA group and 2.9 (SD 1.9) for the no-LA group (p=0.9).

Summary: In patients with Dupuytren’s contracture treated with collagenase injection, administering local anesthesia before the collagenase injection significantly reduces the patients’ pain experience.
Effect of Delayed Finger Extension on the Efficacy and Safety of Collagenase Clostridium Histolyticum Treatment for Dupuytren’s Contracture

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Hypothesis: The current labeling for CCH indicates that the finger extension procedure should be performed 24 hours after injection. The effect of varying time to finger extension was evaluated as part of a study of patients who received two concurrent injections of CCH to concurrently treat two affected joints of the same hand.

Methods: A total of 715 patients with >=2 contractures in the same hand caused by palpable cords participated in a 60-day, multicenter, open-label phase 3b study. Patients received two CCH doses (each 0.58 mg) injected into one or two cords in the same hand during the same visit. Finger extension was performed 24, 48, or >=72 hours later. Changes in fixed flexion contracture (FFC) and range of motion (ROM), rates of clinical success (FFC <=5°), and adverse events (AEs), were summarized by time of finger extension (24, 48, or >=72 hours).

Results: In the study, 725 joint pairs were treated; among these pairs, 268 (37%) had finger extension at 24 hours, 299 (41%) at 48 hours, and 158 (22%) at >=72 hours. A total of 714 patients and 724 joint pairs were analyzed for efficacy. Improvement in FFC and ROM at 30 days post-CCH injection and clinical success rates were similar regardless of time to finger extension (Table 1). A similar percentage of subjects experienced >=1 treatment-related AE regardless of time to finger extension; the majority of AEs began on the day of injection or finger extension. Most AEs were mild to moderate and resolved without intervention.

Summary:
- Concurrent injections of CCH to treat two Dupuytren’s contractures on the same hand were effective in reducing contracture and increasing ROM; the safety profile was consistent with what has been reported in previous studies.
- The timing of the finger extension procedure did not affect clinical response in terms of efficacy or safety, although numerically, the rate of lacerations appeared lower when finger extension was performed at 72 hours rather than at 24 or 48 hours.
- The ability to vary the time between CCH injection and the finger extension procedure may allow for greater flexibility for both physicians and patients.

Table 1. Efficacy Outcomes at 30 Days After Concurrent CCH Injections to Treat Two Dupuytren’s Contractures, by Time of Finger Extension Procedure

<table>
<thead>
<tr>
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<th>Finger Extension at 24 h (n=268)</th>
<th>Finger Extension at 48 h (n=298)</th>
<th>Finger Extension at &gt;=72 h (n=158)</th>
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<tbody>
<tr>
<td>Total FFC, mean % change (SD)</td>
<td>75.2 (25.2)</td>
<td>74.8 (24.5)</td>
<td>72.5 (24.9)</td>
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<tr>
<td>Total ROM, mean change (SD), degrees</td>
<td>66.7 (31.3)</td>
<td>67.9 (31.9)</td>
<td>64.0 (32.3)</td>
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<tr>
<td>Clinical success (FFC &lt;=5°), n (%)</td>
<td>213 (65.5)</td>
<td>237 (62.9)</td>
<td>129 (66.5)</td>
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<tr>
<td>MP joints</td>
<td>62 (29.4)</td>
<td>70 (32.0)</td>
<td>26 (21.3)</td>
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<tr>
<td>PIP joints</td>
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The use of a dynamic dorsal splint for Dupuytren Rehabilitation after collagenase.

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Hypothesis: Post-operative rehabilitation is an important phase in the management of Dupuytren's disease. Treatment should be directed toward restoring hand function and monitoring development of complications that could compromise the outcome.

Method: We analyzed 30 patients with Dupuytren contracture treated at Hand Surgery Department of Universital Hospital of Verona (Italy) during the last 2 years. All included cases (26 men and 4 women, age between 54 and 72) were grade 1 and 2 of Tubiana classification. All cases were treated with the collagenase enzyme protocol in a single finger. 10 had a PIP contracture and 20 a MP one.

All patients started rehabilitation protocol the day after the extension manipulation. Randomly they were divided into 2 groups. The first group (15 patients,) used a custom made dorsal rigid splint in full extension; dynamic graduated full extension was allowed according to patient’s compliance and pain with a simple tape. Second group (15 patients,10 MP and 5 PIP contracture) used a volar static rigid splint, weekly modified in full extension by hand therapist. Splint was prescribed for 22 hours/day, with only 2 hours of active and passive full range of movements for 21 days; afterwards only during the night for 6 weeks more. Movements were allowed for 2 hours/day associated with skin massage.

The two groups were compared analyzing the recovered R.O.M., the active extension of the finger and compliance of the splint support since day 2 after post-collagenase manipulation until 30 days after definitive splint removal.

Results: After 4 weeks both group showed a good R.O.M. recovery. The group with dorsal splint (group 1) showed a faster improvement in the recovery of the extension compared to the volar one.

We suggested that this faster recovery is due to the harder extension traction or the dorsal dynamic splint compared with the simple volar static one. The dorsal splinting leave the volar side of treated fingers free for dressing for possible skin lesions or for use of elasticizing creams. Patients with the dorsal splint reported a better feeling and compliance during daily activity compared with the volar group (Figure). No painful or negative events were detected.

Summary: Dorsal dynamic splint used 22hours/day showed a faster and improved extension recovery during rehabilitation in Dupuytren disease after collagenase protocol and it’s more comfortable for patients during the whole treatment and daily activities.
Treatment with Collagenase Clostridium Histolyticum: Five-Year CORDLESS Data

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Background: CORDLESS (Collagenase Option for Reduction of Dupuytren’s Long-term Evaluation of Safety Study) is a five-year noninterventional follow-up study to determine the long-term efficacy and safety of collagenase Clostridium histolyticum (CCH) treatment for Dupuytren contracture.

Methods: Patients from previous CCH clinical studies were eligible. Enrolled patients were evaluated annually for contracture and safety at two, three, four, and five years after their first injection (0.58 mg) of CCH. In successfully treated joints (≤ 5° of contracture following CCH treatment), recurrence was defined as either ≥ 20° of worsening (relative to Day 30 after the last injection) with a palpable cord or any medical or surgical intervention to correct new or worsening contracture. A separate, comparative post-hoc analysis in which worsening was defined as a change of ≥ 30° was also performed.

Results: Of 950 eligible patients, 644 (with 1081 treated joints) were enrolled. At five years, recurrence was observed in 47% (291) of 623 successfully treated joints (39% [178] of 451 metacarpophalangeal [MP] joints and 66% [113] of 172 proximal interphalangeal [PIP] joints). Based on the alternative threshold of ≥ 30°, worsening was observed in 32% (198) of the 623 (26% [119] of the 451 MP joints and 46% [seventy-nine] of the 172 PP joints). A total of 105 secondary interventions (17%) were performed in the successfully treated joints; 47% (forty-nine) of these involved fasciectomy and 30% (thirty-two) involved additional CCH. One mild adverse event was attributed to CCH treatment. Antibodies to clostridial type-I and/or II collagenase were found in 93% of patients, without discernible clinical import.

Conclusions: Five years after successful CCH treatment, the overall recurrence rate of 47% was comparable with published recurrence rates after surgical treatments. One long-term treatment-related adverse event was reported. CCH injection therefore represents an effective and safe treatment for Dupuytren contracture. Both repeat CCH treatment and fasciectomy were elected by patients who received additional treatment during follow-up.
Prospective Multicenter, Multinational Study to Evaluate the Safety and Efficacy of Concurrent Collagenase Clostridium Histolyticum Injections to Treat Two Dupuytren’s Contractures in the Same Hand.

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Hypothesis: This study was conducted to evaluate the safety and efficacy of concurrent administration of two collagenase clostridium histolyticum (CCH) injections into cords in the same hand to concurrently treat two joints with Dupuytren’s fixed flexion contractures (FFC) with palpable cords.

Methods: A total of 715 patients with ≥2 contractures in the same hand caused by palpable cords participated in a 60-day, multicenter, open-label phase 3b study. Two 0.58-mg CCH doses were injected into one or two cords in the same hand (one injection per affected joint) during the same visit. Finger extension was performed 24-72 hours later. Changes in FFC and range of motion (ROM), rates of clinical success (FFC ≤5°), and adverse events (AEs) were summarized.

Results: In this study 714 patients and 724 joint pairs were analyzed for efficacy and safety. Joint pairs treated included metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints on the same finger (48%), two MP joints (34%) or 2 PIP joints (10%). At 30 days following injection, mean total FFC (sum of two treated joints) decreased 74%, from 98° to 27°. Mean total ROM increased from 90° to 156°. Clinical success (FFC ≤5°) was reached in 64.6% of MP joints and 28.6% of PIP joints. The most common treatment-related AEs were edema peripheral, contusion, and pain in extremity. The majority of treatment-related AEs were mild or moderate in severity. Sixteen patients reported ≥1 treatment-emergent SAE; 6 patients experienced SAEs considered treatment-related or possibly treatment-related, including 1 anaphylactic reaction that resolved with treatment in the emergency room and 1 tendon rupture (fifth finger flexor digitorum profundus rupture) that occurred during finger extension).

Summary:
- Compared with reported results of phase 3 clinical trials (using ≥3 injections/joint, administered as single doses sequentially at 4 week intervals), the current study (using a single injection in each of 2 affected joints, administered concurrently) showed similar efficacy and a similar frequency of most AEs except skin lacerations, which were more frequent in this study.
- These results support those of two previously conducted studies, demonstrating that CCH can be used to effectively treat 2 affected joints concurrently, without a greater risk of AEs compared with treatment of a single joint.
- Two concurrent CCH injections may allow more rapid overall treatment of multiple affected joints, without the need to wait ~4 weeks between treatments as required in the approved labeling.
An Open-label, Controlled Phase 2a Study of the Safety and Efficacy of Injectable Collagenase Clostridium Histolyticum (CCH) in Patients with Adhesive Capsulitis (Frozen Shoulder)

Marie Badalamente, Edward Wang, Sean MacKensie, Michael Skyhar, Gregory Kaufman, Ted Smith, Yan Ling, Diane McCaul, James Tursi; Stony Brook University Medical Center, NY, 11794, USA, + other loc.

**Hypothesis:** Adhesive capsulitis (AC), a painful, progressive shoulder condition, results in loss of range of motion (ROM) in the glenohumeral joint. Collagenase clostridium histolyticum (CCH, Xiaflex®) is approved for the treatment of adults with Dupuytren contracture with a palpable cord. A proof-of-concept study suggests that further evaluation of CCH as potential nonsurgical treatment option for AC was warranted. This phase 2a, open-label, controlled, dose-ranging, multicenter study was designed to assess the safety and efficacy of CCH injection(s) compared to an exercise-only control group in patients with Stage 2 (frozen) unilateral idiopathic AC.

**Methods:** 50 patients (10 male, 40 female) at 11 sites throughout the USA with a mean age of 54 years (range, 41-74) were enrolled. Patients were aged ≥18 years, with Stage 2 (frozen) unilateral idiopathic AC for 3-12 months before the screening visit. Inclusion criteria were restricted total active ROM (AROM) deficit of ≥60° in all planes, and a deficit of ≥ 30° as compared with the contralateral shoulder in one or more of the following planes: forward flexion, abduction, or external/internal rotation. Four cohorts of 10 patients each received up to 3 ultrasound-guided extra-articular injections, directed onto the anterior capsule, of 0.29 mg or 0.58mg of CCH (in varying volumes: 0.5, 1, or 2 mL), separated by 21 days. After 1% lidocaine injection onto the anterior capsule for local anesthesia, the CCH dose was injected through the same needle track using a spinal needle. Cohort 5 (n=10) performed home shoulder exercises only. All patients (cohorts 1-5) were instructed to perform the same home shoulder exercises, three times per day. The primary endpoint was change, in degrees, from baseline to Day 92 in AROM forward flexion in the affected shoulder compared to the exercise-only cohort. Secondary endpoints were change from baseline to Day 92 in 3 additional planes (abduction, external/internal rotation). Function and pain were assessed using the American Shoulder and Elbow Surgeons scale. Adverse events (AEs) were assessed at every visit. Baseline and end of study Day 92 shoulder MRIs were obtained for all patients.

**Results:** The 0.58 mg/1 mL and 0.58 mg/2 mL dosing arms showed significant improvement from baseline in AROM forward flexion vs. the exercise-only group (P=0.0131 and P=0.0385, respectively). Trends with improvement in AROM were also seen in the other CCH treated cohorts. Twenty-nine patients (72.5%) received 3 CCH injections, 5 patients received 2 injections, and 6 received 1 injection. Both the 0.58 mg/1 mL and 0.58 mg/2 mL cohorts had significant improvement in pain and function from baseline vs. the exercise-only group (P<0.05). Treatment-related AEs with CCH were most commonly transient and confined to
local injection site. AEs of injection site pain and injection site swelling resolved in ≤7 days without intervention. There were no serious AEs. Baseline and Day 92 MRI evaluations indicated that there were no clinically significant rotator cuff injuries or other safety findings.

**Summary:** Extra-articular injection of CCH (1 mL and 2 mL) significantly improved ROM, shoulder function and pain compared to an exercise-only treatment regimen in patients with AC. The safety profile was consistent with a prior study¹ and CCH use in other indications. Further clinical trials are ongoing to evaluate the potential merit of CCH in patients with adhesive capsulitis.

Collagenase - what we may never know - a discussion paper

David Warwick, University Hospital Southampton, SO16, United Kingdom.

Xiapex (CCH) effectively reduces Dupuytren’s contracture with prompt recovery and minimal morbidity. Some healthcare systems will not consider CCH without reliable data comparing the treatment with Percutaneous Needle Fasciotomy (PNF) (cheaper) or limited fasciectomy (more risk but less recurrence).

Hypothesis: We proposed that a valid generalisable unbiased randomised trial cannot be designed because:

- **Heterogeneity of disease**
  - Cords suitable for CCH may not be suitable for PNF (e.g. broad cords and some cords at PIP level)
  - Very discrete cords at MCP level are more suitable for PNF
  - Some recurrent cords or those in patients with diathesis are probably more suitable for dermofasciectomy

- **Absent equipoise**
  - An RCT can only be undertaken ethically if both clinician and patient have equipoise for both treatments.
  - In our experience, 4/5 patients requesting CCH would never agree to surgery. So recruitment will be impaired by patient bias.
  - Different surgeons feel that different cords are suitable for different treatments.

- **Suitable outcome measures**
  - The most appropriate outcome measures vary between treatments and cannot be readily balanced.
  - A functional score specific to Dupuytren’s has not been validated.
  - Expense is challenging to calculate. The societal cost savings from rapid return to work with PNF or CCH is not readily factored in the health care cost to the payer of health care.
  - Complications - severity and frequency.

- **Funding**
  - An RCT requires funding. The cost is unlikely to be supported by a pharmaceutical company. A state funded trial would, in the absence of a robust protocol, be unlikely to receive funding in competition for the same funds towards a more generalizable study.

- **Blinding**
  - A randomised trial should, whenever possible, be blind to outcome from the perspective of the patient and the investigator. This will not be feasible when comparing PNF, CCH and LF.
• **Recurrence as an outcome measure**
  o This poses a particular problem. There is no accepted definition of recurrence. A recurrence may hold different value after different treatments. For example a recurrence after PNF or CCH might be readily treated again with a simple needle technique or by surgery that has not been rendered difficult by the initial treatment; recurrence after previous LF is a complex and more risk prone procedure. So a lower recurrence rate after surgery may be offset by the complexity of treating that recurrence.

• **Duration of follow up**
  o Although recurrence can discriminate between CCH, PNF and LF, the measurement of recurrence needs prolonged follow up - probably 5 years. Such a long follow up poses challenges with funding, loss-to-follow up and currency of the study. A study would take two years to analyse and publish, so 7 years from inception. Healthcare systems, patients, surgeons and indeed the pharmaceutical company which has underwritten drug development, marketing and distribution costs might reasonably expect to use CCH in a considered manner without waiting for this duration.

**Summary:** There are certain aspects about Xiapex which we will have to deduce and cannot prove.
Controversies 3:

The best minimally invasive treatment for Dupuytren Disease: PNF or Collagenase?

Chair: Charles Eaton

Percutaneous Needle Fasciotomy: Paul Werker

Collagenase injection: David Warwick
Elevated cAMP Inhibits both Basal- and PDGF-Induced Cell Migration and Contraction in Dupuytren’s Contracture-Derived Fibroblasts

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Hypothesis: We hypothesized that increased levels of cyclic AMP (cAMP) in Dupuytren’s contracture-derived fibroblasts would reduce both cell migration and contraction.

Method: Fibroblasts harvested from actively diseased Dupuytren’s contracture cord (DC) and from the adjacent grossly unaffected palmar fascia in the same patients (PF) were compared to fibroblasts derived from the palmar fascia of carpal tunnel (CT) patients. Cells were subjected to an in-vitro wound healing “scratch” assay to measure cell motility into the denuded zone; photographs were taken at 0h and 48h and the distances migrated were quantified. Cell contraction was determined using the stressed fibroblast populated collagen lattice (sFPCL) contractility assay. FPCLs were allowed to develop mechanical stress (24 hours), treated with PDGF (2ng/mL) and/or forskolin (10 μM, a known cAMP inducer), released, and allowed to contract over a period of 6 days.

Results: We found higher basal motility in DC-fibroblasts compared to unaffected palmar fascia (PF-) and CT-derived fibroblasts. PDGF stimulated cell motility in all three populations, and the addition of forskolin inhibited both basal and PDGF-induced cell migration in all three cell types. Interestingly, the inhibitory effect of forskolin on PDGF-induced cell migration was more pronounced in DC-derived fibroblasts compared to the other two cell types. Western blot analysis showed that neither PDGF nor forskolin exposure had any effect on phosphorylation of p38 and PI3 kinase in DC-derived fibroblasts. Both forskolin and PDGF increased p42/44 MAP kinase phosphorylation. Notably, elevated cAMP resulted in increased RhoA phosphorylation and a subsequent decrease in the level of activated RhoA in DC-derived fibroblasts.

We also found that DC-derived fibroblasts have significantly higher inherent contractile ability than CT-derived fibroblasts, with PF-fibroblasts intermediate in their contractility. These findings confirmed our previous observations using relaxed FPCL (rFPCL) assay. PDGF enhanced the contractility of PF- and CT-derived fibroblasts, but had little effect on DC-derived fibroblasts. Exposure to cAMP inhibited both basal- and PDGF-stimulated contraction in all three cell types, but the effect was most prominent in DC-derived fibroblasts.

Summary:
- These results again indicate that unaffected palmar fascia in DC is host to cells that are intermediate in phenotype between CT control and actively diseased DC cells.
- These results for the first time examine DC fibroblast motility and suggest that cAMP may be a useful agent to modulate DC fibroblast behavior and possibly forestall disease progression and recurrence.
- Although not specific to the cell type, stimulation of cAMP most prominently inhibited the contractility of DC-derived fibroblasts.
Correlation of function with deformity in Dupuytren’s Disease- the condition specific Southampton Scoring Scheme outperforms the generic QuickDASH

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Introduction: Patient Related Outcome Measures should now be an integral part of hand surgery practice but they must accurately reflect the underlying condition. The QuickDASH (QD) is widely used across Hand Surgery but many of the domains (e.g. tingling, pain, sleep) are not affected in Dupuytren’s Disease (DD) which is likely to affect its validity. The Southampton Dupuytren’s Scoring Scheme (SDSS) has just five domains, each relevant to Dupuytren’s Disease. We aim to confirm the validity of the SDSS.

Hypothesis: That the SDSS correlates with deformity better than the QuickDASH

Methods: 297 patients with DD completed both the QuickDASH & SDSS simultaneously just prior to treatment. Total deformity was measured with a goniometer.

Results: QD did not correlate with deformity ($r=0.04$, $p=0.65$) whereas SDSS correlated modestly ($r=0.19$, $p=>0.001$).

Summary: Whilst a condition specific score (SDSS) has better validity than a generic score (QuickDASH) in DD, nevertheless the correlation between deformity and function remains moderate. Other factors, rather than deformity alone, may have greater determination for the functional effect of DD.

Reference
Poster

**Tonometry as an outcome measure for the treatment of Dupuytren’s disease.**

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**Hypothesis:** Early DD can be treated in a variety of ways, including Intralesional steroid injections and radiotherapy, but there are no objective ways of assessing disease regression. The current literature relies on clinical examination of palmar nodule consistency. An objective non-invasive measure of tissue pliability that can be used as an outcome measure to effectively compare clinical interventions is required.

**Method:** Tonometry has been used clinically to evaluate tissue hardness of cutaneous scars and lymphoedema. The resistance of tissues to compression is measured using a durometer, a hand-held mechanical gauge which is rested against the patient’s skin. Patients with Dupuytren’s disease and healthy volunteers were recruited prospectively to a clinical trial to determine whether tonometry can be used to distinguish between the hardness of palmar nodules in patients with Dupuytren’s disease and palmar skin of healthy volunteers at an equivalent site. Ethical approval was obtained and all recruited patients gave informed written consent. Tissue hardness was measured using a durometer and scored from 0-100 with 100 being the hardest reading possible. Two independent assessors measured all patients using an agreed standardised protocol to minimise inter-observer variability. Each assessor was blinded to the score recorded by the other. Three measurements were taken and the mean score recorded.

**Results:** Thirty seven participants were recruited to the study: 25 patients with Dupuytren’s disease and 12 healthy volunteers. The healthy volunteers were matched for gender and age to patients with Dupuytren’s disease. The ages of the healthy volunteer (mean ± SEM, 61.4 ± 3.1 years) and the patients with Dupuytren’s disease (64.5 ± 2.1) were similar, as was the ratio of male to female patients in both groups (3:1).

<table>
<thead>
<tr>
<th></th>
<th>Dupuytren’s disease, affected hands only (mean ± SEM)</th>
<th>Healthy volunteers, both hands (mean ± SEM)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonometry</td>
<td>Mean 52 ± 1</td>
<td>Mean 29 ± 1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Inter-observer reliability was high as assessed by calculation of the intraclass correlation coefficient of 0.96 (95% confidence intervals 0.942 to 0.967) p <0.0001.

**Conclusion:**
- The hardness of palmar nodules in patients with Dupuytren’s Disease can be measured by a rapid, simple, and inexpensive tonometry test
- Further research is needed to evaluate the use of tonometry as an objective outcome measure for patients with early Dupuytren’s disease.
**Poster**

**Intra- and inter-observer agreement on diagnosis and measurements of Dupuytren disease severity**

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**Introduction**: Dupuytren disease (DD) is a fibrosing disease affecting the palmar aponeurosis, and is mostly treated by surgery based on measurements of severity of the disease. Literature concerning the measurement reliability is scarce. This study aimed to determine the intra- and inter-observer agreement of four variables for diagnosing DD and its severity. One of them is a new measurement on the area of nodules and cords for measuring the severity in early stage of the disease.

**Methods**: Both hands of 54 participants were independently investigated for the presence of DD by two trained investigators. If present, the nodules and cords were encircled with an erasable skin pencil, whereafter the area of nodules and chords was determined using a tumorimeter (fig 1). Additionally, the Tubiana stage and total passive extension deficit (TPED) was determined using a goniometer (fig 2). Agreement was calculated based on an intraclass correlation coefficient (ICC) using a latent variable model on subjects for diagnosis and Tubiana stage. For TPED and the area of nodules and cords, agreement was calculated with an ICC using a one-way random effects model with subject as random effect. Agreement for each variable was determined per finger.

**Results**: Inter-observer agreement was very good for diagnosing DD (ICC: 95.5 – 99.9) and good to very good for classifying Tubiana stage (ICC: 73.5 – 94.9). Agreements for area and TPED were moderate (middle finger) to very good (ICC: 48.4 – 98.6 and 45.0 – 99.5, respectively). Intra-observer agreement was slightly higher on average than inter-observer agreement.

**Conclusion**: Overall, the intra- and inter-observer agreement in diagnosing DD and determining its severity is high. Also, the newly introduced variable area of nodules and cords has high intra- and inter-observer agreement, indicating that it is suitable to measure disease severity.

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**Figure 1. The tumorimeter**

**Figure 2. The goniometer.**
**Variation in range of movement reporting in Dupuytren’s disease.**

Anna Pratt, Catherine Ball; Brunel University London, UK; Kennedy Institute of Rheumatology, University of Oxford, UK.

**Hypothesis:** Range of motion is the most commonly reported outcome used to evaluate interventions in Dupuytren’s disease however, there is considerable variation in how this measure is reported. The lack of consistency in range of motion reporting prevents comparison between studies and pooling of data for meta-analysis. Method: We systematically reviewed the literature with the aim of establishing robust methodology for measuring and reporting range of movement for Dupuytren’s disease in future studies. Following a PICOS analysis for primary or recurrent Dupuytren’s disease range of motion, a systematic search of databases for the last 20 years (Ovid Medline, Ovid EMBASE, CINAHL, PubMed) was carried out using pre-determined search criteria:

<table>
<thead>
<tr>
<th>PICOS Analysis</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Dupuytren’s Disease of the hand.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Surgical treatment/percutaneous fasciotomy/collagenase injection for DD</td>
</tr>
<tr>
<td>Comparisons</td>
<td>Not applicable (systematic review)</td>
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<tr>
<td>Outcomes</td>
<td>Reported range of motion</td>
</tr>
<tr>
<td>Study design</td>
<td>Included: - RCT’s, non-randomised CCT’s and case series.</td>
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<tr>
<td></td>
<td>Excluded: - Case studies, reviews and conference papers.</td>
</tr>
</tbody>
</table>

Following further screening, 90 studies met the inclusion criteria. Results A total of 24 different descriptors were used to describe range of motion in the 90 studies. While some studies measured and reported active range of motion, others reported passive motion or were unclear. Furthermore it was not always clear how range of motion was measured, with goniometry reportedly used in only 43 of the 90 studies. The most frequently reported range of motion measures were percentage change, flexion contracture and joint contracture, with 29 authors using more than one measure. Percentage change was reported in 19 studies. However, without access to raw data, percentage change lacks context and does not allow direct comparison of baseline characteristics. Eight of the 24 categories were identified as possibly describing the same measure, ‘lack of joint extension’. A clear description of what is being measured within the methodology section of each research article would have confirmed this. Range of motion methodologies that require summed calculations such as Tubiana grading and total active motion do not identify at which joint changes in motion occur.

Summary We found that published studies lack clarity in reporting range of motion, preventing data comparison and meta-analysis. Based on our findings we recommend that range of motion measuring and reporting for Dupuytren’s disease requires standardisation:

- Range of motion should be measured following a recognised assessment protocol such as American Society of Hand Therapists.
- A goniometer with a minimum of 2 degree graduations used.
- Active flexion and extension of individual joints should be assessed and recorded.
- Documenting passive PIP joint extension with the MCP joint flexed will identify fixed flexion deformities and shortening of volar soft tissues.
- Aggregate scores e.g. Tubiana and Total Active Movement should only be used in addition to reporting individual joint range of motion.
- The same technique should be used to measure and report range of motion before and after treatment.
**Experience of treating patients with stage IV of Dupuytren's contracture**

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**Hypothesis:** Treating patients with IV stage of Dupuytren's contracture is a complicated and topical task of modern hand surgery. This is due to the high risk level of different complications after surgery (altogether about 76%) and high level of unsatisfactory treating results (more than 40%).

**Goal of study:** Improving results of treating patients with Dupuytren's contracture by creating an algorithm of choosing optimal options of surgical procedures based on clinical positions.

**Materials and methods:** We have studied results of treating 214 patients with 4-th stage of Dupuytren's contracture by R. Tubiana classification. Patients were divided into two groups based on the procedure. On the patients in the group 1 (127 patients) needle aponeurotomy was performed in outpatient conditions. After operation we have reached summary correction of one finger joints to 90-100 degrees. In postoperative period stage correction of the remnant contracture with the help of individual orthosis made of thermoplastics with daily increasing of the extension angle to 5-10 degrees. Additionally complex physiotherapy based on using phonophoresis with fermencol (complex of collagenase). Immobilization in the maximum extension position during night time was conducted until 5 weeks post-operation. To 56 patients with manifest node degeneration of palmar aponeurosis injection of collagenase (fermencol) or steroid hormones were made during the aponeurotomy. Full functional recovery appeared on day 14-21. To 21 patients with the quick relapse of disease (under 6 month) subtotal resection of aponeurosis was performed.

All patients of group 2 (86 patients) received subtotal aponeurotomy with the use of microsurgical equipment. In the postoperative period all patients received reconstructive therapy. Primary correction of flexion contracture did not surpass 100 degrees. After fixating the finger with the k-wire we were able to perform 140-150 degree correction. Wounds were closed primarily with the use of different methods of skin plastics with the local tissues. Time of hospital treatment 4-7 days. Function recovery 4-20 weeks.

**Results:** Rating of the treatment results was made with the qDASH point system. Time of observation made up to 6 years after operation. In all patients of both groups full correction of flexion contracture in metacarpophalangeal joints was achieved, but in proximal interphalangeal joints remnant arthrogenic contractures up to 9 degrees in group 1 and 20 degrees in group 2 often were present. Complications in group 1 were: ruptures and deep skin splits (9%), in group 2 - border skin necrosis (48%) and neurodystrophic syndrome (35%). Amount of suppurative complications was low in both cases – 3.9% in 1 and 5.6% in 2. One patient (0.25%) from group 1 had iatrogenic damage of flexor tendon in zone 2. Great results -56.4% (group 1) and 18% (group 2) observations, good in 28.1 (1) and 15% (2), satisfactory in 10.4% (1) and 40% (2), unsatisfactory in 5.1% (1) and 27% (2). Relapse was observed in 42% (1) and 7.5% (2).

**Summary:** Received data shows high sufficiency of two stage in treating patients with IV stage Dupuytren's contracture.
Hypothesis: In recent years, a new minimally invasive technique of treating Dupuytren's contracture - Needle Aponeurotomy - has prevalence in the world. The essence of this technique is percutaneous dissection of the affected aponeurosis cords on a number of levels through small punctures with the help of different-sized needles. The aim of study is to capture results of treating patients suffering from Dupuytren’s contracture via operation by the new minimally invasive technique - Needle Aponeurotomy.

Materials and methods: We quote the experience of using Needle Aponeurotomy in the Department of (REMOVED FOR ANONYMITY) from 2007 to 2013. In 6 years 783 Needle Aponeurotomy were performed to 659 patients with Dupuytren's contracture with all stages of it, where 141 operations (18%) were 1st stage, 196 (25%) - 2nd stage, 258 (32.9%) - 3rd stage and 188 (24.1%) - 4th stage (R.Tubiana classification).

In order to lower the risk of traumatizing common and digitalis propria arteries all patients were examined with high frequency Doppler ultrasound (20 MHz). Needle Aponeurotomy was performed under local infiltration anaesthesia as outpatients or on a day-case regime (3rd-4th stage). Additionally steroid hormones (kenalog, diprospan) were injected in the cords and nodes of palmar aponeurosis, collagenase preparations (collalysin), in some cases lipofiling was performed.

Patients proceeded to moderate physical activity on the next day after treatment, hard work possible on day 2-10. In the postoperative period to all patients with severe degree of illness (IIIrd-IVth) were performed paraffin applications and phonophoresis with fermencol, finger fixation in maximum extension position with the help of gypsum splints or thermoplastic orthosis.

Results: Rating of the treatment results was made with qDash point system and integral index of hand function (by professor (REMOVED FOR ANONYMITY).). Time of observation was from 6 months to 6 years. Almost full correction of extension contracture in metacarpophalangeal joints but in proximal interphalangeal joints residual contracture up to 9° often was preserved. Amongst complications skin breaks and cracks were dominant 70 cases (9%), digitalis propria artery damage 58 (7,4%), wound suppuration 13 (1,7%), twice iatrogenic damage of flexor tendons took place. Great results were obtained in 442 (56,4%), good – 220 (28,1%), in 81 (10,4%) - satisfactory and unsatisfactory in 40 (5,1%). Relapse was confirmed in 305 cases (39%) and that required second minimally invasive operation and subtotal resection of palmar aponeurosis 33 (4,2%). Average time of relapse took 2,1 years.

Summary: Thus obtained results allow us to make a conclusion about high efficacy of using this technique to treat different aged patients with any stage of Dupuytren's contracture. Wherein with elder patients (older than 70 years) with heavy somatic pathology this technique could be advised as the operation of choice due to lesser traumatizing and shorter recovering time.
**Poster**

**YAP1 is a driver of myofibroblast differentiation in normal and Dupuytren’s fibroblasts**

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**Hypothesis:** YAP1 is a transcriptional co-activator, and the main output of the Hippo signalling cascade, and was recently shown to be activated by TGF-β1, a pro-fibrotic growth factor. We hypothesized that YAP1 plays a role in regulating the differentiation of dermal fibroblasts into highly contractile myofibroblasts, and in the maintenance of a contractile and synthetic phenotype in Dupuytren’s myofibroblasts.

**Methods:** To investigate the role of YAP1 in myofibroblasts we performed esiRNA mediated knockdown of YAP1 in human dermal fibroblasts and primary Dupuytren’s myofibroblasts. Transfected dermal fibroblasts were stimulated with TGF-β1 (10 ng/mL) to induce myofibroblasts. We analysed gene expression of ACTA2, COL1A1, CCN2, YAP1, and a panel of genes involved in the collagen biosynthesis pathway. Protein levels of SM α-actin, collagen type I, vinculin, and F-actin were analysed by immunofluorescence staining and immunoblot. Transfected cells were seeded on fibronectin-coated silicone substrates, or in a collagen hydrogel to study their contraction capabilities. Matched affected and control tissues from Dupuytren’s patients were co-stained for YAP1 and SM α-actin. Statistical analysis was performed using GraphPad Prism version 5.03.

**Results:** We found that YAP1 is activated during TGF-β1 induced myofibroblast differentiation, as seen by its nuclear translocation. Knockdown of YAP1 prevented the formation of SM α-actin fibres, and prevented the deposition of fibrillar collagen type I (despite an increase in COL1A1 mRNA levels). Interestingly, we did not find an aberrant expression profile of genes involved in the collagen biosynthesis pathway. Furthermore, we showed that YAP1 deficiency suppressed the formation of a contractile phenotype in myofibroblasts, but did not affect the formation of F-actin fibres. By translating our findings to a clinical relevant model, our data revealed that YAP1 deficiency in Dupuytren’s myofibroblasts resulted in decreased expression of SM α-actin and collagen type I. Finally we showed that YAP1 levels are elevated in affected Dupuytren’s tissues, and that the expression pattern partly co-localizes with SM α-actin positive cells.

**Summary:**
- Our data showed that YAP1 is a major regulator of myofibroblast differentiation in TGF-β1-induced myofibroblasts.
- YAP1 is crucial for the maintenance of a contractile and synthetic phenotype in Dupuytren’s myofibroblasts.
- YAP1 is highly elevated in affected Dupuytren’s nodule tissue, and partly co-localizes with SM α-actin positive cells, suggesting a role for YAP1 in the pathology of Dupuytren’s disease.

**DISCLOSURE:** This work was financially supported by the Netherlands Institute for Regenerative Medicine (NIRM). Part of this work was performed at the UMCG Imaging and Microscopy Centre (UMIC), which is sponsored by NWO-grant 40-00506-98-9021. BH receives funding by the Canadian Institutes of Health Research (CIHR) (grants #210820 and #286920) and the Collaborative Health Research Programme (CIHR/NSERC) (grants #1004005 and #413783).
Clinical validation of pharmacoeconomic model in Dupuytren Contracture
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Hypothesis: Dupuytren's contracture (DC) is usually managed with partial fasciectomy (PF). Recently placing Clostridium histolyticum collagenase (CCH) into market as a new treatment. It is described a simple tree decision model to compare both treatments. No clinical validation has been formally done. The aim of our study is a clinical validation of a new decision tree to collect the types of complications that can occur in each of the treatments.

Method: We compare two decision trees used to compare the surgical treatment and the CCH in DC. Model 1 is the simplest; reflects the success or failure of therapy and complications generally the same. Model 2 provides more detail the types of complications. For clinical validation of both models, we used a survey that includes the following six attributes: structural simplicity, comprehensibility, adaptability, reliability, extrapolation to other countries and applicability.

For a better understanding of both models, they were previously explained by an orthopedic surgeon before the questionnaire was wait on. The mean scores were analyzed using the t test for paired samples. To check the consistency of scores Cronbach's alpha was performed and the interclass correlation coefficient to measure the degree of agreement.

Results: The questionnaire to assess the models was answered by 27 orthopedic surgeons; 11 of them (40.7%) were first-level hospitals, 8 (29.6%) to secondary care hospitals and 8 (29.6%) remaining to tertiary care hospitals. Only five residents responded to the survey and the rest of surgeons have any available mean of practitioner like specialist of 10.1 (minimum: 0; maximum: 30) years. Not missing data were collected from surgeons in our questionnaire.

Globally, Score Total obtained was 35.81 (CI95%: 32.58-39.05) for model 1 and 39.44 (CI95%: 36.46-42.43) for model 2. Scores differences were, model 2 vs model 1: structural simplicity -3.03 (p<0.05), comprehensibility -2.44 (p<0.05), adaptability 3.52 (p<0.05), reliability 3.63 (p<0.05), extrapolation to other countries 0.74 (p=0.23) and applicability 1.22 (p=0.10). Therefore there were no significant differences between the scores given to both models. Nor different results are analyzed separately by the hospital level of care they belonged surgeons or his experience as a practitioner.

The internal consistency of the scores was moderately high; Cronbach's alpha based on standardized items was 0.741. The correlation coefficient interclass (average measures) to assess the agreement between the two models was 0.614 (95% CI: 0.392 to 0.788), and for consistency was 0.727 (CI95%: 0.546 to 0.857) both being statistically significant (F = 3.661; P <0.05).

Summary: Our results show that both models studied could be considered equivalent. However, the model 2 appears to be more reliable and adaptable than model 1, which is simpler and understandable. The clinical validation of a pharmacoeconomic model is possible in DC and is a prerequisite for its use in pharmacoeconomic studies.
Collagenase versus fasciectomy in Dupuytren disease: cost-utility analysis

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Hypothesis: To evaluate the efficiency of Clostridium histolyticum collagenase (CCH) comparatively with partial fasciectomy (FSC) in a single hospital. The aim of our study is to determine which option is more cost-effectiveness for treatment of Dupuytren’s contracture (DC), PF versus CCH, in our hospital for a follow-up to 6 months.

Method: Cohort study with historical control group, FSC patients, and case group, CCH patients. Data on CCH injections were collected prospectively. 91 patients were included in the study; 43 FSC and 48 CCH. Both groups were comparable statistically. The effectiveness was defined as a reduction in the degree of contracture of the 66% at least, measured as a percentage of the initial contracture with regard to the contracture end. We only use one infiltration of CCH per finger.

The utilities were assigned to 8 and 6 health scenarios for FSC and CCH, taking into account the possible complications. The study perspective was the healthcare system. All relevant direct medical costs for both alternatives were collected in €, year 2014. Unit costs were obtained from the Pharmacy Service and Accounting Department of the Hospital. Efficiency is measured as cost-utility ratio (ICUR) by patient equal to incremental cost divided by incremental utilities. An analysis of sensitivity by modifying the main variables to check the robustness of the results was performed.

Results: FSC was effective in 87.50% and CCH was 67.44% in the patient. Complications and recurrences (18.75% and 14.58% FSC, 18.60% and 11.63% CCH) were similar in both groups. The main cost of the CCH group was drug costs (62.45%). In the FSC group, however, the costs were more divided: 28.5% operating room, 19.7% physical therapy, 13.9% recurrences and 13.6% anesthesia.

Mean cost by patient obtained was FSC group 1420.19€ (CI95%: 1127.64-1709.65) and CCH group 1161.72€ (CI95%: 1034.35-1317.71). The mean utilities obtained was 0.9892 (SD: 0.0050) and 0.990 (SD: 0.0064) QALYs for FSC and CCH respectively. ICUR was -293766€/QALY. The sensitivity analysis of key variables and tornado diagram shows the robustness of our results. Only cost of vial’s drug could change ICUR above to threshold (30000€/QALY).

Summary: After following patients during 6 months, CCH was more efficiency than FSC in DC treatment of single finger at our hospital.
**Poster**

**Origin of Dupuytren’s myofibroblasts in an ex vivo tissue culture system**

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**Hypothesis:** Excess accumulation and proliferation of myofibroblasts is by definition the main contributing pathological factor in Dupuytren’s disease. However, the exact origin of myofibroblasts remains unknown. Our hypothesis is that connective tissue myoepithelial stem cells serve as precursors of Dupuytren’s myofibroblasts.

**Method:** Biopsies were obtained from the diseased nodules, excluding fat and skin tissue overlying the nodule, from primary resection DD specimens. We assessed the expression of selected stem cell markers by immunofluorescence, RNA seq and fluorescence-activated cell sorting (FACS). FACS sorting experiments were performed to obtain single cells expressing stem cell subpopulations. Single cells were either maintained in vitro in matrigel cultures or were transplanted into DD decellularized tissue which was maintained in an ex vivo three-dimensional tissue culture method.

**Results:** RNA sequencing data indicate upregulation of stem cell-identity transcripts in DD specimens compared to fibroblasts derived from carpal tunnel or synovium tissue. The DD RNA sequencing signatures are enriched in expression both TGFβ and Wnt pathway members; this was further validated by FACS and immunofluorescence. We have identified a distinct stem/progenitor cell subpopulation in DD that is negative for myofibroblast marker expression (fibronectin, αSMA) and positive for stem cell markers (Lgr5, Nanog, Tdgf-1). The differentiation potential of this cell population towards myofibroblast phenotype is being investigated in decellularized DD extracellular matrix.

**Summary:**
- We have identified a distinct cell population with stem cell characteristics in the DD nodular tissue.
- Characterization of this unique population has been accomplished using single cell isolation in combination with novel ex vivo culture methods. Single sorted (FN-/Lgr5+) cells are maintained long-term in defined matrigel cultures.
- Proliferation and plasticity towards myofibroblast is routinely tested in 3D ex vivo tissue culture system (decellularized DD matrix).
- Ultimately, ex vivo genetic and molecular manipulation of this cell population might provide insight on the recurrent pathology of DD and lead to new therapeutic advances.
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