Dupuytren Disease and Related Diseases – The Cutting Edge

Paul M.N. Werker
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Charles Eaton
Bert Reichert
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Editors

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Preface

This is the second book that follows an international Dupuytren conference organized by the International Dupuytren Society and the Dupuytren Foundation. The first book was published following the conference in Miami in 2010. The new book entails the content of the international meeting dedicated to Dupuytren Disease and related fibromatoses, which was held in Groningen, the Netherlands, in May 2015. The editors are grateful for the amount of work the authors were willing to put into preparing their book chapter. Some papers presented in Groningen are missing and will appear in indexed journals. Some chapters from authors, who were not able to participate in the Groningen conference, have been added.

This book offers an excellent overview of the most recent findings in both basic and clinical Dupuytren and related fibromatoses research. The content of this book is organized in ten parts, each devoted to a theme and also containing papers on controversies in which authors present their scientific view on a controversial topic.

All chapters have been peer reviewed by at least two experts in the field in a similar fashion as journals do, and we are grateful to the following section editors and reviewers for helping us to achieve the highest scientific level.

Marie Badalamente, New York, USA
Steve Coleman, Brisbane, Australia
Tim Davis, Nottingham, UK
Ilse Degreef, Leuven, Belgium
Charles Eaton, West Palm Beach, USA
Dominic Furniss, Oxford, UK
Hans Hennies, Cologne, Germany
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Ulrich Lanz, Munich, Germany
David O'Gorman, London, Canada
Bert Reichert, Nuremberg, Germany
Heinrich Seegenschmiedt, Hamburg, Germany
Paul Werker, Groningen, The Netherlands.

How far have we advanced since the 2010 Miami meeting?

Unfortunately, there is still no cure for Dupuytren Disease or any of the other fibromatoses. But this book will disclose the latest advances: there is promising new insight into the genetic basis, the pathophysiology of the

diseases is increasingly better understood, and new ideas for the cessation of the progression have been raised and tested in the laboratory. Clinical testing will be the next step to prove their curative value. At the same time, we have entered an era in which less invasive treatments have conquered a significant role in most countries. Notwithstanding this, some unfortunate patients still suffer from recurrent contractures of especially the PIP joints, while some patients lose fingers as the result of damage inflicted during repetitive surgery. More and more, and helped by patient organizations, do we understand what really is important for the patients and how we can help them the best.

The last part of this book discusses strategies for fostering future research, for further improving international collaboration, for setting new directions, for better funding, and for finding "future paths of research."

All these topics are covered in this book and it also reflects the spirit toward more multidisciplinary engagement of all scientists working in the field, which was one of the major outcomes of the Groningen symposium. We sincerely hope you will enjoy reading this book as well as hope that it will bring across some of this multidisciplinary enthusiasm!

Groningen, The Netherlands	Paul Werker
Leicester, UK	Joe Dias
West Palm Beach, FL, USA	Charles Eaton
Nuremberg, Germany	Bert Reichert
Übersee, Germany	Wolfgang Wach

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Editor's Biography

Paul Werker Professor Werker studied Medicine at Utrecht (NL), Aberdeen (UK), and Harrow (UK) and graduated in 1987. He thereafter fulfilled his compulsory Military Service at the Military Hospital in Utrecht and finished his duty as Captain. He completed a PhD on free flap preservation in 1992 and trained at the University Medical Centre of Utrecht to become a plastic surgeon in 1996. He was Fellow in reconstructive microsurgery in Louisville KY, USA, before returning to Utrecht as an Assistant Professor. In 1999 he became an attending plastic surgeon in Zwolle (NL) and moved to Groningen (NL) in 2006, where he is currently Professor and Chair of the Department of Plastic Surgery of the University Medical Center Groningen.

Professor Werker is a diplomate of the European Board of Plastic Reconstructive and Aesthetic Surgery (EBOPRAS) and the Federation of European Societies for Surgery of the Hand (FESSH). He is a member of the Dutch Society for Plastic Surgery, the Dutch Society for Hand Surgery, the Dutch Society for Aesthetic Plastic Surgery, the British Society for Surgery of the Hand (BSSH), the European Association of Plastic Surgeons (EURAPS), and the American Association of Hand Surgeons.

Professor Werker is (co-)author of 86 peer-reviewed PubMed listed journal papers and 14 book chapters and co-editor of a book entitled *Dupuytren's Disease and Related Hyperproliferative Disorders* and has won the Esser prize for his work on the foreskin free flap in 2000. His clinical areas of interest are Dupuytren's Disease, reconstructive surgery of breast, and facial palsy. Dupuytren's Disease is his most important research line at the University Medical Center Groningen

Joe Dias is Professor in Hand and Orthopaedic Surgery and Head of Academic Department of Musculoskeletal Surgery at the University Hospitals of Leicester. He is also a Consultant Hand and Orthopaedic Surgeon for the University Hospitals of Leicester. He graduated from Bombay University with a Bachelor of Medicine and Bachelor of Surgery (MBBS) degree. He has since received Fellowships from the Royal College of Surgeons in Edinburgh and England and a Doctorate of Medicine from Leicester University.

He has a special interest in epidemiology in hand and wrist disorders, Dupuytren's contracture, and the outcome of interventions in upper limb and hand trauma and interventions in wrist disorders. His research has focused on clinically based investigations of effectiveness of interventions for hand and upper limb disorders. He has a special interest in education.

He has published over 152 scientific articles, over 20 other publications, and 27 chapters in books most on hand surgery. He has 24 publications on scaphoid fractures. He has authored multiple national reports and NICE accredited clinical pathways.

He was Editor-in-Chief of the Journal of Hand Surgery (Europe edition) and on the Editorial Board for the Journal of Bone and Joint Surgery.

Professor Dias was President of the British Society for Surgery of the Hand (BSSH) in 2008 and was President of the British Orthopaedic Association (BOA) in 2012. He is a member of international societies FESSH, IFSSH, and the Indian Society for Surgery of the Hand. He was Head of School of Surgery at the East Midlands Healthcare Workforce Deanery (South) and currently oversees a research team, with five MD/PhD students and two BSc students at the University of Leicester.

He is Chair of the PbR Tariff for Trauma and Orthopaedic Surgery in the UK and also chairs the EWG on T&O HRGs. He was Chair of the Clinical Commissioning Guidance development group and on the boards of the UK Department of Health Enhanced Recovery and Shared Decision Making programs.

He is Chair of the University Hospitals of Leicester NHS Trust Clinical Senate.

Charles Eaton, MD is a hand surgeon in West Palm Beach, Florida, USA. He is the founder and Executive Director of the Dupuytren Foundation, a US nonprofit organization. Dr. Eaton worked in academic and private practice and developed a Dupuytren-centered practice. He closed his practice in 2012 to volunteer full time for the Dupuytren Foundation. He has authored articles and textbook chapters on a range of hand surgery topics, with an emphasis on Dupuytren Disease. Dr. Eaton's daily focus is the International Dupuytren Data Bank research project which he established and continues to develop. Dr. Eaton has early Dupuytren disease, first diagnosed after he co-authored the 2012 textbook "Dupuytren's Disease and Related Hyperproliferative Disorders". He serves on advisory boards of the International Dupuytren Society, the British Dupuytren Society, and the Canadian Dupuytren Society.

Reichert Bert finished Medical School in Hannover, Germany, in 1984 to join the military service as medical officer for 1 year. Starting in 1986 he specialized in general, plastic, and hand surgery at Hannover Medical School. In 1998 he became deputy director of the Department of Plastic and Hand Surgery at Lübeck University. In 2004 he was appointed Director of Plastic, Reconstructive and Hand Surgery at Nuremberg General Hospital. In 2014 Nuremberg became the second campus of the Paracelsus Medical University. Dr. Reichert was appointed Professor and Chair for Plastic Surgery.

Dr. Reichert is author of numerous publications and book chapters, chair member of German Hand Society (DGH) and the German Society of Plastic, Reconstructive and Aesthetic Surgery (DGPRÄC), past President of the German Burn Society (DGV), and member of several other scientific societies. He is also on several editorial boards and a court-appointed expert.

His major fields of interest apart from Dupuytren Disease are microvascular reconstruction and treatment of burns and its sequelae.

Wolfgang Wach received his PhD in Solid State Physics from the University of Munich, Germany. After 6 years of research in ion implantation, he worked in integrated circuit design at Siemens and Honeywell, and as General as General Manager at AT&T Microelectronics Europe. He started his own software company CAL in 1995 and the Dupuytren Society in 2003. The International Dupuytren Society IDS is a nonprofit organization with patients and physicians from all over the world cooperating in informing about Dupuytren Disease and its therapeutical options, in supporting patients, and in finding a cure for Dupuytren Disease. Wolfgang Wach is a patient and one of the chairmen of the International Dupuytren Society and of the Deutsche Dupuytren-Gesellschaft (German Dupuytren Society).

Part I

Epidemiology and Patients Views

Bert Reichert and Paul Werker

Treatment of Dupuytren Disease in Different Countries: A Welcome Address from the President of IFSSH

1

Zsolt Szabó

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1.1 Introduction

When I was asked to deliver the opening lecture of this very promising and highly scientific congress, my first thought was that, based on my experience in working with the delegates of different national societies from Europe (FESSH, Federation of European Societies for Surgery of the Hand) and the world (IFSSH, International Federation of Societies for Surgery of the Hand), I would create a questionnaire. I would include general questions about the epidemiology, treatment, complications, recurrences, and final outcome of the patients treated in their country. As good as this idea seemed as difficult it was to know whether or not it would receive realistic, scientifically valuable data. As time advanced and the congress approached, I realized that although it might be possible to review a large pool of data reflecting theoretical knowledge of the group, I started to have concerns whether it would be useful and interesting as a first lecture of such an event. Finally, I decided instead that I would present my subjective feelings based on my experience. Maybe the statements will be lacking exact numbers and facts, but they will reflect exactly what I feel, what I think, and what I believe in my usual funny, sometimes ironic way of summarizing certain situations. I would like to apologize if I hurt someone's feelings or if my statements are too generalizing and do not fit, but my purpose is not to offend or criticize anybody, only to express

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my personal feelings and provide a friendly open-minded atmosphere of this great scientific and teaching event.

1.1.1 History (My Personal History)

When I first entered in a hand surgery operation theater, I was a young medical student, and the famous plastic surgeon of the hospital was operating on a hand with contracted fingers. I saw and understood almost nothing, and I could not imagine how it was possible to find those small little structures, the nerves and arteries in that hard tissue block without hurting them. After this first admiration immediately came a great disappointment: the operation was finished with a big open wound in the palm, without even attempting to close it. I remember thinking that I would definitely not be happy to have this in my own palm. That time I was not even thinking of becoming a hand surgeon, but life sometimes takes interesting turns. I have seen myself travelling from a politically isolated Eastern European country to be a resident in Stockholm's Karolinska Institute and to Guy Foucher's SOS Main Strasbourg Clinique, followed by years in Nice University Hospital and in Showa University in Tokyo. I have learned a lot. I have learned how to do things and how not to do things. It was difficult to accept, but I have seen that what was white in one part of the world was black on the other side with different grays in the middle. In 1997 in Bologna, during my oral examination for the European Diploma Examination, Professor Safar asked me about the operation of a Dupuytren-contracted PIP joint, about the relations of the Grayson and Cleland ligaments, and about the importance of the spiral cord and what to do with the checkreins. If I would like to summarize my opinion of the first 10 years of hand surgery concerning Dupuytren Disease, I would say that this is one of the most exciting conditions of the hand solved in different manners, with different skills and techniques. If I would like to make a quick opinion on a hand surgeon's skills, this would be the first operation I would like to see him perform.

1.1.2 Years of Tranquility (The Calm Before the Storm)

As the scientific chairman of the 2004 Budapest IFSSH Congress, I noticed that hand surgeons like Dupuytren Disease. There were many abstracts for free papers and a large number of attendance in the lecture rooms. Dupuytren is just like football and politics: everyone is an expert. In the last decades, there was great interest but no historical discoveries, no revolutionary changes, and no unsolvable controversies. Dupuytren Disease was a calm sea in the middle of the ocean of hand surgery. There were some basic research articles dealing with the histopathology of the disease but without great interest for the everyday practitioner. When I became chairman of the European Diploma Examination, it became clear during the evaluation of the examination results that Dupuytren Disease is one of the favorite topics of the candidates. That was the perfect question when the examiner wanted to help the candidate.

1.1.3 Rebirth of Dupuytren Disease (The Start of a Mild Revolution)

When a group of European hand surgeons from different countries and different strategic positions were invited by a medical drug company (Pfizer) for a whole day brainstorming session and the subject of the discussion was an injection which would solve the contracture and replace surgery, nobody thought that this event/drug would definitively change our view and knowledge on Dupuytren Disease. Dozens of serious concerns were listed, and a significant opposition was detected against the original material, method, and outcome prognosis. The surprising outcome of this meeting was that for the first time in the history of hand surgery, a medical drug company was interested in the opinions of the specialists and, even more importantly, took them seriously. An advisory board was formed and our initial concerns were taken in consideration. New and more detailed

data on the drug was provided. Instructional materials were replaced. The importance of training was accepted. Authorization to use the drug was restricted to medical staff that had experience in the treatment of the disease. Clinical studies were considered and started. However, the real value of the collagenase injection was that starting with its commercial introduction, in almost all major hand surgical events, FESSH and IFSSH congresses, national congresses, and courses, a symposium or a workshop or a session dealing with Dupuytren Diseases was included. The good thing was that these sessions not only dealt with the "new" treatment method but also relaunched the research on the etiology on the different treatment methods, on the outcomes, and on the recurrences of the disease. We should not underestimate the financial contribution of the drug-selling company to the budget of these scientific events directly contributing to the teaching value of these events and the positive influence on basic and clinical research sponsored by them. Due to this, Dupuytren Disease became in the focus of every organization dealing with hand surgery, and every hand surgeon wanted to have information on this new treatment method.

1.1.4 The Actual Situation (Calm After Storm)

Introduction of the drug in different countries and geographic regions was completely different due to different regulations and different economics. There were countries where it was a simple procedure and everybody was happy, countries where the hand surgeons were against it, and countries where the financial situation made the treatment with the drug unaffordable. Financial interests of surgeons afraid of replacing the income of a big operation by the smaller remuneration of a simple injection coupled with the understanding that this injection was not the wonder tool to solve every Dupuytren Disease forever resulted in a very colorful situation on the international map of hand surgery. The drug company itself realized that this was not the biggest financial success story, that the benefit was less than expected, and that the large amount of spent money with education and marketing would probably never come back. The growing and more clear data on the recurrence rate, possible complications, and adverse reactions made it possible to have a more realistic view on the real value of the collagenase. Only in the future, when more detailed well-planned clinical studies with prospective data are collected, will we be able to define the real value and position of different treatments in Dupuytren Disease. Today we try comparing apples with pears; we mix what we think with what we believe and what we know, sometimes spiced up with a hint of what we hope. Because evidence-based data are replaced sometimes with eminence-based data, it is very difficult to be objective and eliminate subjectivity. Because it is a very difficult, almost impossible task, I will not even try, but instead will summarize my subjective feelings on this very challenging and favorite topic.

1.2 Etiology

If you look around the world, you will understand that the interest toward this disease varies. There are countries where the majority of older males have this disease and others where you can find this disease only among the representatives of the Scandinavian consulates. If you ask about the etiology, the majority will tell you that this is a genetically determined, inherited "Viking" disease, but will give no precise explanation of what gene is responsible, how is it inherited, or how the Viking ancestors reached those far from the sea remote places. One interesting answer regarding the etiology of the disease was: "I don't know exactly but anyway it has no interest for me. Most important is that this disease is generating the highest percentage of the income of my practice." It seems that every existing and nonexisting human behavior and pathological condition has been associated in a way or another to Dupuytren Disease. Microtraumas related to hard physical work, alcohol, and epilepsy are the most common etiological factors, but only a few hand surgeons know and speak about the existence and importance of the diathesis.

1.3 Histopathology

Every course, congress, and symposium dealing with Dupuytren Disease usually start with detailed high-level studies dealing with the different forms and stages of fibroblasts and the different types of collagen. “Real-life” understanding of Dupuytren Disease is a little bit simpler and to my great surprise spans from the occasional belief that it is contracture of the flexor tendons (!) to the most frequent idea that it is collagen cords generated by fibroblasts. It may seem surprising that a surgeon treating Dupuytren thinks that this is a contracture of the flexor tendons, but it was even more surprising for me when in one patient I found during a reoperation a repaired state-of-the-art central cord according to Bunnel flexor repair with core and circumferential suture dating from a previous “not too successful” operation for Dupuytren Disease. Another interesting intraoperative finding I have seen after a previous operation was the total absence (!) of the superficial and deep flexor tendons in the fourth and fifth rays.

1.4 Diagnostic

For the majority of surgeons in the majority of the world’s countries, making the diagnosis of Dupuytren Disease is one of the simplest things: it needs “just a look.” On the other side, in some very fancy, “sophisticated” centers, we hear about ultrasound, MRI, or histological examinations for the diagnosis of this condition.

1.5 Treatment

Finally, we are arriving at the most interesting and challenging piece of cake: the treatment. There are several aspects which commonly arise when discussing treatment modalities in different stages of the disease. The most frequently discussed question regarding treatment is who should treat the condition.

1.5.1 Who?

The question is whether a GP or rheumatologist is authorized or not to treat the disease. In some countries, rheumatologists or GPs without any specific knowledge on the anatomy, pathology, and possible complications bravely deal with percutaneous needle aponeurotomy. In other countries, general surgeons, trauma surgeons, orthopedic surgeons, or plastic surgeons deal with the condition. In some countries, a national diploma of hand surgery is needed. The latest improvement in specializations provides us a country where the European diploma in hand surgery is needed to surgically treat Dupuytren Disease. During my pilgrimage around the world, the most generally accepted (and for me the most reasonable idea) is that only a person who is able to deal with the resolution of any eventual complication is entitled to treat a certain condition.

1.5.2 Where?

The question where to treat a patient with Dupuytren Disease may seem simple and without any controversy, but depending on the local habits, national regulations, financing, and tradition, this varies from ambulatory outpatient care to at least one week hospitalization. Discussing this question, we may agree that the tradition, the level of civilization, the presence of the social network, and education of the patients considerably influence the place of treatment.

1.5.3 When?

Despite the very well-established and proven fact that surgical treatment in early nodular stages does not give the best outcomes, we always find surgeons who think that surgical treatment should start as early as possible. A series of nonsurgical alternative treatment modalities may argue for an as early as possible treatment, but the generally accepted rule seems to be to recommend treatment when the patient is limited in his everyday activities by the condition.

1.5.4 What?

Treatment of Dupuytren Disease varies in countries around the world from acupuncture, ultrasound, light therapy, massage, and even meditation to the clear and simple argument of treatment with surgery. Medical treatment has been reported a few times, but no clear and evidence-based results have been reported on the usefulness of a drug. Steroids, anti-inflammatory drugs, cytostatics, enzyme inhibitors, and several other drugs have been tested, but no relevant data has been reported. The only useful alternative therapy in incipient stages seems to be radiotherapy. The majority of hand surgeons know about this therapy but never use it, have no idea on the treatment details, and are concerned by the eventual complications and adverse effects of the radiotherapy. Needle fasciotomy became a minimally invasive competitor to surgery but never became generally accepted and available. In the last years, the use of collagenase entered like an explosion. Everybody knows about it; lots of people use it; those who have only heard about it all would like to try it. Those who have never tried it have the most precise opinion about the "theoretical" disadvantages of the method, giving one the feeling that they are trying to explain why they have never tried it. But speaking about the treatment of Dupuytren Disease, we must admit that the significant majority of hand surgeons agree that the treatment of the condition should be a surgical one.

1.5.5 Surgery

Surgery varies from the simplest "just break the cord" and leave everything as it was to the very last possibility of amputation of the involved ray. Depending on what to do with the cord (cut it and leave it there; cut it and take it out; take it out together with the surrounding healthy tissue), we have different types of surgery. Depending on what we do with the skin and the probable skin defect, options range from simple Z-plasties to multiple Z-plasties and open-palm techniques to replacement of the skin defect with split-thickness or full-thickness skin grafts. Every method has its advantages and its adepts. Every surgeon is convinced that their methods are the best, safest, and most beneficial for the patient.

1.5.6 Postoperative Care

If surgery is controversial and provides us a multitude of options, postoperative care also divides hand surgeons in two big groups. One group says that the only advice of postoperative care should be: "use your hand as early and as much as you can." The members of the other group are convinced by the usefulness of splints and think it is mandatory to use a day and night splint during the first weeks after the operation followed by a nighttime splint for weeks and months after surgery. There are others who think that dynamic splinting will improve their results. Surprisingly, despite the fact that a large majority of surgeons are aware of the evidence that there is no significant difference in outcomes between groups with postoperative splinting and without splinting, they still continue to follow their own previous habits.

1.6 Complications

The number or percent of complications show very interesting variations. There are surgeons who believe that they have no complications. Others report significant numbers of injured nerves, tendons, and CRPS. It is very difficult to express the complication rate in one number or percentage, because it is different depending on the stage of the disease, whether it is a new disease or a recurrence, and the experience and skill of the operating surgeon. The most frequent intraoperative complications are injuries of nerves and arteries. Early postoperative complications include hematoma formation, pain, swelling, and bleeding. Late postoperative complications include wound-healing problems, limitation of range of motion, chronic regional pain syndrome, long-term

numbness, and paresthesia. Usually there is general agreement that not the complication itself causes the real long-term problem but rather when it is missed or neglected and no repair or treatment is performed to solve the complication.

1.7 Prognostic

Prognostics vary, depending on the self-confidence, ego, and knowledge of the surgeon, from the confident "healed forever" to the pessimistic "we can do whatever, but the disease will come back."

1.8 Recurrences

Recurrences are one of the most controversial topics in Dupuytren Disease. At this moment there is no clear definition on what should be considered recurrence. The appearance of a new nodule or a cord in an already operated area or reappearance of an extension deficit of 10–20–30° is the most frequent subjects of discussion. As we go back in reading historic articles, we may see that the older the publication the lower is the recurrence rate. This is probably not due to earlier times having better or more skilled hand surgeons, but due to the fact that data collection and study methodology in the past had more deficiencies. Another very interesting conclusion when listening to different hand surgeons around the world is that the majority of recurrences and severe complications are always coming from the famous "elsewhere hospital." After attending several scientific meetings dealing with recurrences in Dupuytren Disease, my conviction is stronger than ever that recurrences seem to be a problem for the scientist and for the surgeon but not for the patient. It seems that satisfaction of the patient is not related to the percentage of recurrences, and first of all when reoperating for a recurrence, the main indication should be the limitation in activities and the will of the patient.

1.9 Future

It may seem futuristic, but probably the final solution will be a pill that will make the disease disappear. When applying any kind of treatment to our patients we should inform them that we cannot treat the disease itself but only its manifestations. Once we know the exact genetic basis of the disease, genetic surgery might possibly solve the problem. Dupuytren Disease might just be another case like duodenal ulcer, a condition which was one of the most frequent operations for general surgeons 30 years ago and almost completely disappeared in our days due to the discovery and treatment with proton pump inhibitor drugs.

1.10 Conclusions

If I have to list a series of conclusions, the most relevant for some countries around the world I would conclude in the following way:

- In the USA, they are clever. They developed the collagenase treatment. They use it and they sell it, making lots of money.
- In Scandinavia, they are rich, so they buy and use collagenase.
- In France, hand surgeons fight with rheumatologists whether or not to use needle fasciotomy. They don't like collagenase as it is American, and they are convinced that the best way to treat Dupuytren Disease is to do a fire break dermofasciectomy.
- In Germany, they are brave and not afraid of radiotherapy. They don't believe in collagenase because there are no comparative studies, and they prefer to buy the drug on the "black market," importing it from Austria.
- In the UK, they do lots of different studies and publish them in their journal written in fluent native English.
- In Netherlands, they want to do something new and they do lipofilling (probably because they have a lot of liposuction), and of course they organize successful high-level Dupuytren congresses.

- In Eastern Europe, we are eagerly looking to the "Big Brothers," and we are ready to do everything which is cheap and available and with which we can earn some money.

1.11 Decision-Making

If everything is so unclear, so different, and full of controversies but everybody wants the best outcome for his/her patients, then how to decide? The most difficult step in evaluating the different data, stories, presentations, teachings, and lectures is to recognize whether those data represent "evidence-based" data or "eminence-based data." We should understand that it is important to know if the presented data are what the presenter believes, knows, or hopes! We may think that evidence-based data are mandatory in our everyday decisions, but reality is different. Decision-making can be regarded as a cognitive mental process, resulting in the selection of a course of action among several alternatives. Every decision-making process produces a final choice. The decision-making is a reasoning or emotional process which can be rational or irrational. As surgeons, we like to think that our decision-making is completely rational, based on evidence. The reality is that medical decision-making is a very complex and very well-studied process. The goal is improved patient outcomes. It is based on three pillars:

(a) Best available clinical evidence
(b) Individual clinical expertise
(c) The patient's values and expectations

Based on the above listed, I am convinced that everything I have written up to this point in this chapter represents my beliefs. Of course, there are things I do not want to believe, but I know are true. These facts are:

(a) Regarding Dupuytren, we really need evidence-based data.
(b) Even if we have evidence-based data, we do not use it as we should.
(c) We have to work a lot, constructing and finalizing studies which may help us to better know the disease.
(d) We have to finally agree on what is a recurrence and what should be considered a complication.
(e) We have to take in consideration our patients' expectations.
(f) Xiapex/Xiaflex development and marketing has contributed enormously to our education and knowledge on Dupuytren Disease.
(g) FESSH and IFSSH are willing to promote knowledge (congresses, courses, committees, reports) and not beliefs among hand surgeons.
(h) Scientific events like this one in Groningen (due to the hard work of the organizers) help a lot to improve our knowledge and the outcome of our patients.

1.12 Final Remarks

Finally, I am convinced that one day our patients will take a pill and there will be not anymore need for surgery, and thus complications and recurrences will disappear. Maybe this will be beneficial for the patient, but then unfortunately the field of hand surgery will be poorer with loss of one of its most interesting chapters.

On behalf of FESSH and IFSSH, I would like to thank all organizers of this event for the great job they have done and would like to express my conviction that the congress in Groningen and this book presenting results from Groningen will prove a great learning experience with a major contribution to our knowledge on the disease.

Conflict of Interest The author has no conflicts of interest to declare.

The Epidemiology of Surgical Intervention for Dupuytren Contracture in England

2

Joseph J. Dias

Contents

2.1 Introduction

Epidemiology for the uninitiated (Coggon et al. 2009) states:

> Epidemiology is the study of how often diseases occur in different groups of people and why. Epidemiological information is used to plan and evaluate strategies to prevent illness and as a guide to the management of patients in whom disease has already developed.

In an amazing study in Haugesund in Norway, Otto Mikkelsen (Mikkelsen 1972) looked at 15,950 subjects and identified a prevalence of Dupuytren Disease in 9.4 % men and 2.8 % of women with a male/female ratio of 3.4. His study would meet most of the requirements of good quality epidemiology in that the population at risk and the definition of the "case" were clearly stated. He also established the increasing rate with age in both men and women and noted the preponderance of right hand involvement in both men and women. Dupuytren Disease is assumed to become symptomatic in men 10 years before women (Ross 1999), although more recent data indicate an average male onset just 4 years earlier (Wach and Manley 2016).

While there is much literature on the epidemiology of Dupuytren contracture, we are still not completely sure about the prevalence or incidence of Dupuytren contracture. There is a considerable variation in the reported rate of prevalence. This is due to three factors, case

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definition, description of the population and the time point (Hindocha et al. 2009).

Firstly, the definition of the case is different for the different papers and varies quite considerably. There is much variation in the case definition (Geoghegan et al. 2004; Hindocha et al. 2009). Many studies use patients presenting to hospital as their cases, and several studies are restricted to patients over 50 where the rate is much higher (Mikkelsen 1972). There is variation on whether the disorder is self-reported, whether the diagnosis is made on a questionnaire, or whether an experienced hand surgeon makes the diagnosis (Hindocha et al. 2009). Many of these considerations have an impact on the reported prevalence rate. Case definition requires two attributes: the description of what constitutes Dupuytren Disease and who assesses it.

The population at risk needs to be clearly described as this forms the denominator and this varies in the different studies reporting prevalence or incidence mainly with regard to the age of the population.

Finally, the period of the study needs clear definition. Even when robust methods are used, there are still very many assumptions made, and the rate declared is usually lower than the true rate. For instance, the calculation of incidence needs the definition of the number of new cases diagnosed in a given year divided by the number of the population at risk without the disease at the beginning of the year. As in many cases the prevalence is not known, it is difficult to have an accurate estimate of the population without the disease at the start of the study period.

Another way to look at the burden of disease is to review the rate of interventions done and use the population served as the population at risk. This ensures that the definition of a case is (a) Dupuytren contracture diagnosed by a clinician who feels that the contracture is sufficient to consider correction (in most cases in England, this will be a contracture that meets the Hueston's Tabletop Test (Hueston 1976)). This reflects the indications described for surgical decisions in Europe in an analysis of 687 surgeons (Dahlin et al. 2013). The population served is the population at risk and will include those that did not present with Dupuytren contracture and those that did.

2.2 Rate of Surgery for Dupuytren Contracture

In England data is collected on every patient that comes into hospital and is admitted for treatment. These form part of the Hospital Episode Statistics (HES) data. The diagnosis is coded using International Classification of Diseases, Tenth Revision (ICD10 WHO disease coding system). In the UK, surgery excises or divides the cord causing finger contracture, and this is the standard established treatment. The procedure is coded using the Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS 4.7) codes which are similar to Diagnostic-Related Groups (DRG) and other systems of procedure codes used in other countries.

In England each procedure done gets a tariff, an amount of money the NHS pays for that procedure. A very small proportion is treated privately and the tariff for these is different. This permits an estimate of cost to treat. For each case, a lot of other data is collected, one such data item is the length of stay in hospital. The population served by each hospital was derived from the UK national datasets. The cost of treatment was calculated from the PbR tariff of the NHS.

Over 2 years, 2010/2011 and 2011/2012[1], around 34,000 patients had Dupuytren contracture release in England. We investigated the procedures done for Dupuytren contracture in 143 NHS hospitals. This data can be explored using funnel plots of rate of surgery. A funnel plot is a type of control plot where on the x-axis there is the population served by each of these National Health Service hospitals and on the y-axis is the rate of operations for Dupuytren contracture per 100,000 population per year. The mean rate line in England is just over 50 per 100,000 population per year. The funnel plot has control lines at 2 and 3 standard deviations away from the mean.

[1] The year is from 1st of April of the first year to 31st of March of the following year.

Fig. 2.1 The rate of surgery for Dupuytren contracture in the 143 NHS hospitals in England. The figure shows the different rates per 100,000 population, not standardised for age or gender. The rate varies remarkably, and there is no clear geographic pattern to suggest different disease burden in different parts of England (This figure is produced in Tableau used with permission from Academic Programs, Tableau Software)

Even adjusting for overdispersion, there are a sizeable number of units outside these control lines. This could reflect the geography of the disease and its severity but could also reflect the different thresholds for offering intervention and the different capacities and expertise available in the units offering treatment. Any health system needs to investigate these reasons further so such variation can be understood and addressed.

The larger units do less surgery (Fig. 2.1) than expected, so their rate is less, and many smaller units do much more surgery than expected. The overall raw rate of Dupuytren surgery is 56 per 100,000 per year, and there is a large variation between units.

We do know that there is a difference in disease prevalence in different countries. The disease is commoner, and possibly patients have greater diathesis (Hindocha et al. 2006) in Northern and Western European countries than in Mediterranean countries (Hindocha et al. 2009). It is thought to be rarer in oriental and African populations (Mitra and Goldstein 1994; Slattery 2010). The geography and disease prevalence do not explain the variation (Birkmeyer et al. 2013; McCulloch et al. 2013) in England with neighbouring units only 25 miles apart having very different rates.

This rate of surgery is very much smaller than the rate of prevalence (0.6–31.6 %) (Lanting et al. 2014) but higher than the incidence (34.3/100,000 men) reported in 2004 (Khan et al. 2004).

2.3 Procedures Done for Dupuytren Contracture and Variation

The commonest procedures for Dupuytren contracture recorded in England (Fig. 2.2) are "fasciectomy", which can be either palmar or digital, with "dermofasciectomy" being quite uncommon.

Figure 2.2 shows the variation of the rate of intervention in the NHS hospitals studied. There is 8 variation rate using the technique described by the Department of Health in the UK (2011). Only 6.8 % had fasciotomy with 45 % having palmar surgery and 37 % having digital surgery. Revision surgery accounted for only 2.8 % of our cases. Dermofasciectomy rate of around 4 % is very small, and it probably reflects surgeon preference rather than evidence.

In England around 17,000 operations for Dupuytren contracture are done each year which cost £61 million per year or €81 million per year.

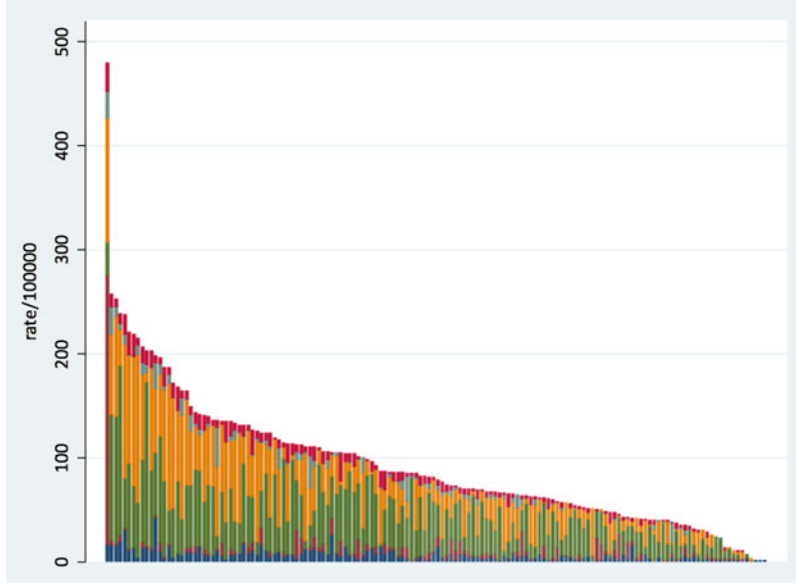

Fig. 2.2 The rate/100,000 in the 143 Hospitals in the NHS in England. The different colours represent different operations for Dupuytren contracture. There is an 8 times difference in the rate of surgery between NHS hospital units in England using the method described in the Atlas of Variation (Figure reprinted from Warwick (2015))

If this data is extrapolated to the 28 European Union countries in 2014 with a population of 507,416,607, we would have 159,854 cases needing treatment for Dupuytren contracture, and if the costs were similar to those in the UK, the annual cost of treatment for Dupuytren contracture in Europe would be €758 million.

A European survey of 687 surgeons established that "fasciectomy" was the commonest procedure with 95 % of surgeons preferring this. A review of 3,357 patient records showed that 90 % of operations were done in patients over 50 years of age (Dias et al. 2013).

There is no change in the revision surgery rate in England. The rate of revision Dupuytren contracture surgery is steady at 2.8 %; it is much less than the expected recurrence of Dupuytren contracture rate in the literature.

Conflict of Interest Statement The author has no conflict of interest to declare.

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Favorite Options of German Hand Surgeons in the Treatment of Dupuytren Disease

3

Bert Reichert and Magnus Baringer

Contents

3.1 Introduction

Percutaneous needle fasciotomy (PNF) in recent years has become well accepted in the treatment of Dupuytren Disease (Eaton 2011; Pess 2012; van Rijssen 2006). Patients accept higher recurrence rates, because morbidity is low and minimally invasive procedures can be repeated in the case of recurrence (Eaton 2012; van Rijssen 2012). Although information on the percentage of surgeons performing PNF and the number of treatments are lacking, it is obvious that in Germany to this day the majority of hand surgeons continue to recommend and exclusively perform various kinds of open surgery.

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3.2 Background

In Germany pricing for newly authorized pharmaceuticals and their reimbursement by statutory health insurance providers are regulated by the Act on the Reform of the Market for Medical Products (AMNOG). If the new treatment is more expensive than established therapies, the critical question is whether there is a proven additional benefit of the new pharmaceutical over established treatments as selected by the Federal Joint Committee (G-BA).

In 2012 the German Institute for Quality and Efficiency in Health Care (IQWiG) performed a benefit assessment for XIAPEX® in the treatment of Dupuytren Disease. It was postulated that it is possible to define treatment options as appropriate comparators in relation to Tubiana stages describing the extent of disease.

For Tubiana stages N/I, I and II percutaneous needle fasciotomy (PNF) was chosen as appropriate treatment, because "various European guidelines and publications" including statements of the German Society for Surgery of the Hand (DGH) have demonstrated that PNF up to Tubiana stage II is "comparably effective" as the markedly more invasive Limited Fasciectomy (LF) (IQWiG 2012).

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During the formal hearing, the representative of the DGH estimated that about 20 % of the members of this society perform PNF, whereas the representative of the pharmaceutical company estimated that only 3.6 % of the procedures performed in Germany are PNF, the rest being fasciectomies.

The representative of the German Society for Plastic, Reconstructive, and Aesthetic Surgery (DGPRAEC) estimated in this hearing that about 30 % of the patients would be eligible for PNF.

3.3 Methods

To find out what their treatment plan for Dupuytren Disease is, we distributed an Internet-based questionnaire to all members of the DGH. Data were collected between January and March 2015.

Participants were asked to answer the questions below:

- How many Dupuytren patients do you treat per year (inpatient/outpatient)?
- Which Tubiana stages do you treat (all stages; II, III, and IV; III and IV; IV)?
- What type of treatment do you prefer in Tubiana stage I (II, III, IV) (LF, PNF, CCH[1], other, none)?
- What are the criteria for your indication (low risk of complication, ease of performance, best outcome, others)?

Descriptive statistics were performed using Microsoft Excel.

3.4 Results

110 of 530 members responded (20.8 %). These members declared to perform in summary 9,761 treatments per year. Since it is estimated that annually approximately 40,000 treatments are taking place,[2] 24.4 % of these would be carried out by the responders. The similarity of these ratios indicates that our questionnaire offers reliable results.

75 % of the patients are treated on an outpatient basis. 40 (36.4 %) of the responding surgeons are treating all patients, regardless of their stage of disease; 53 (48.2 %) are treating only stage II, III, or IV; 16 (14.5 %) are treating only stage III or IV. One surgeon stated that he only treats stage IV cases.

An overview of the preferred methods related to the stage of disease is shown in Fig. 3.1. The data are absolute numbers of surgeons that chose the particular type of treatment as their personal favorite in relation to the stage of the disease.

LF is the favorite option, independent of the Tubiana stage. PNF is being chosen mainly in stages I and II. “Other” summarizes all other treatments that are not CCH, PNF, or LF, e.g., dermofasciectomy. More than 40 % of the surgeons are not treating patients with stage I at all (Fig. 3.1).

One surgeon stated that he treats only 2 cases per year; another one reported treating 400 cases per year. Since this represents a widespread of patient numbers, we defined a coefficient, derived from the number of patients in relation to the whole number of treatments (9,761), and calculated “weighted” treatment numbers.

Figure 3.2 indicates that surgeons treating larger numbers of patients prefer using PNF to a higher degree.

Interestingly, there is a homogenous distribution of case numbers within a subgroup of surgeons that treat up to 100 cases per year, while this is not true for the rest of the responders: those treating more than 100 cases form a heterogeneous group (Fig. 3.3). We therefore performed a subgroup analysis and compared a subset of 5,154 treatments performed by 86 surgeons, doing up to 100 treatments per year, with 4,607 treatments, performed by the remaining 24 surgeons.

The most impressive difference between both groups is in the comparison of preferred treatment options in Tubiana stage II: those performing more procedures favor PNF to a higher degree (Fig. 3.4). In other stages, preferences are very similar. Probably the higher number of PNF is

1 *Clostridial collagenase histolyticum.*

2 www.dupuytren-online.de, assessed September 2015.

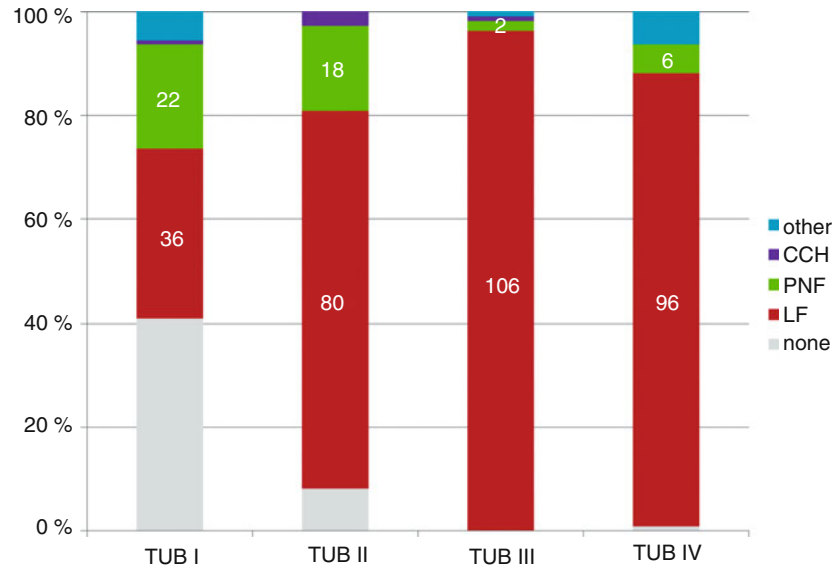

Fig. 3.1 Surgeon's preferred choice of treatment depending on stage of disease

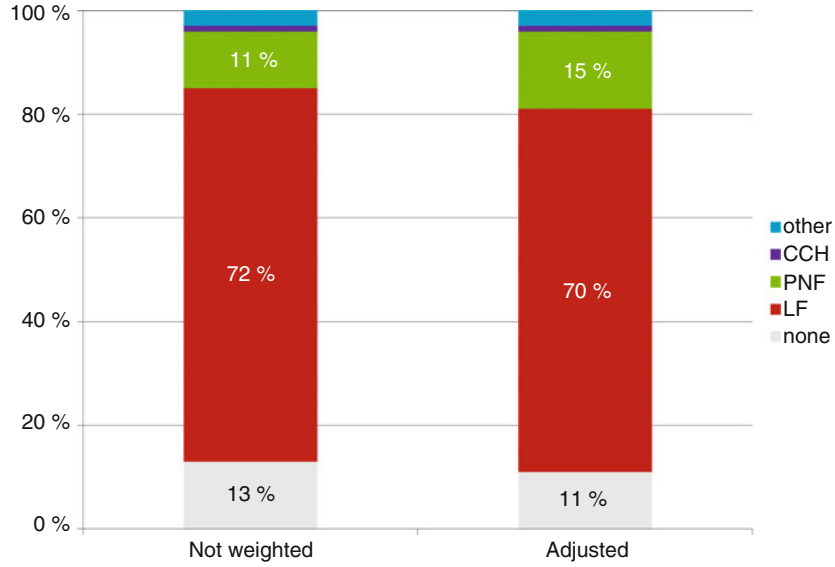

Fig. 3.2 Influence of treatment numbers (all Tubiana stages)

among the reasons why the percentage of one-day cases is significantly higher in the group with more than 100 treatments per year (30.1 %) than in the other one (19.9 %).

3.5 Discussion

Historically, although German hand surgeons were familiar with the fact that PNF was among the options for treating Dupuytren contracture, the vast majority of them originally was skeptical about it. With Albrecht Meinel's presentation of his first experiences at the annual congress of the DGH in 2008, interest rose, and a small group of German hand surgeons began PNF treatment. Promising reports in the German literature and increasing influence by patient organizations further increased the interest in this treatment option (Meinel 2008).

Nevertheless this survey is proving that today still a relatively small number of patients are being

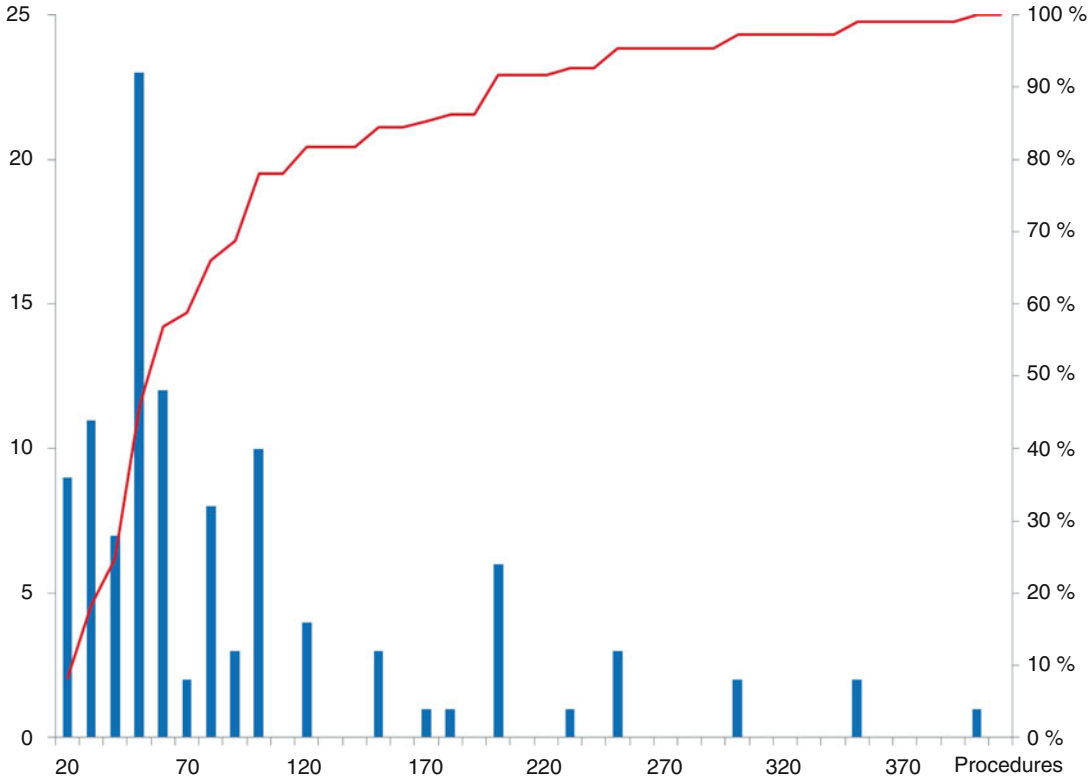

Fig. 3.3 Distribution of treatment numbers

treated with this method. This is remarkable considering that the G-BA has decided in 2012 that PNF is the standard procedure in early stages of the disease (IQWiG 2012).

It can be estimated from our data that about 15 % of treatments of Dupuytren contracture in Germany are PNF and that up to 20 % of German hand surgeons state that they do perform PNF. Also, surgeons treating larger numbers of patients are using PNF to a higher degree, especially in Tubiana stage II disease. Furthermore, those surgeons have a larger amount of outpatients.

Interestingly the estimated percentage of surgeons performing percutaneous needle fasciotomy in Western Europe (France, Germany, the Netherlands, the UK) is 40 % and higher than in any other part of Europe, whereas only 41 % of these surgeons are satisfied with the procedure, which is the smallest percentage compared to the rest of Europe (Dias et al. 2013). The skepticism that we found in our study is reflected in this publication. Having in mind that there is probably a strong bias in that sense that surgeons performing PNF will probably have supported our survey to a higher degree than those who are in opposition to the treatment, our estimations probably are overoptimistic.

Conclusion

PNF has been proven to be effective and safe. Since there is a high potential for this method, efforts should be made to further promote it among German hand surgeons. PNF should become part of instructional lectures and courses which are held by the DGH twice a year.

Acknowledgment and Conflict of Interest Declaration
The authors would like to thank the German Society for Surgery of the Hand (DGH) for supporting this survey. The authors have no conflict of interest to declare.

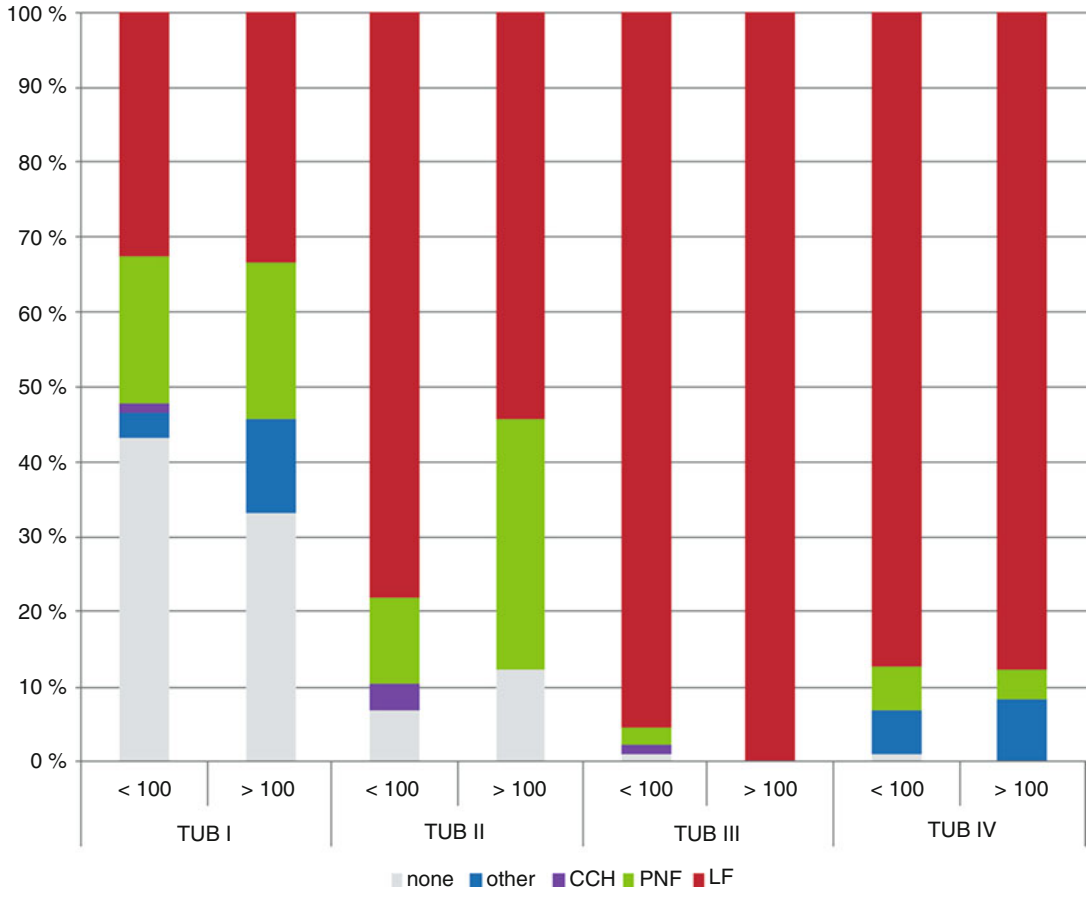

Fig. 3.4 Preferred treatment options depending on the stage of disease and comparison of subgroups defined by treatment numbers

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Trends in Dupuytren Treatment in the United States

4

Scott Hadley, Emerson Floyd, John Zhao, and Philip Blazar

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4.1 Introduction

Since 1777 when Henry Cline first dissected a hand with DC and described its treatment with open fasciotomy, there has been considerable variation in the treatment of Dupuytren contracture (Elliot 1988a). Interestingly, that same year marked the birth of Baron Guillaume de Dupuytren, the French physician-scientist whose name would be coupled to the disease. In 1831, while he was chief of surgery at the Hotel Dieu in Paris, Dupuytren presented two patients with palmar fibromatosis which many point to as the sentinel lecture on the topic (Elliot 1988b).

The standard surgical treatment in the 1800s was closed fasciotomy with a pointed bistoury as first described by Sir Astley Cooper, a pupil of Henry Cline at the end of the eighteenth century (Cooper 1823). In 1865, John Lister's introduction of antiseptic technique to the operating theater would set the stage for an explosion of surgical treatment options for DC. These options included open fasciotomy, limited fasciectomy, extensive fasciectomy, open-palm technique, and dermofasciectomy. In 1993, practice shifted back toward a closed surgical approach with the modern description of closed fasciotomy or needle aponeurotomy (NA) by Badois and Lermusiaux (Badois et al. 1993). Prior to the approval of CCH, all successful treatments for DC were surgical.

Multiple nonsurgical treatments have been attempted, including radiotherapy, ultrasonic

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therapy, dimethyl sulfoxide injections, topical vitamin A and E cream, physical therapy, corticosteroid injections, 5-fluorouracil treatment, and gamma interferon injections (Bulstrode et al. 2004; Ketchum 2000; Knobloch et al. 2011; Pittet et al. 1994; Richards 1952; Vuopala and Kaipainen 1971). Most of these treatments proved to be ineffective, and some were not safe for clinical use. Radiotherapy demonstrated promise in slowing disease progression and remission in early stage disease, but it is not viable as sole treatment for late-stage disease (Betz et al. 2010; Seegenschmiedt et al. 2012).

However, collagenase enzymes have proven to be both efficacious and safe in the treatment of DC. In the early twentieth century, it was observed that culture filtrates from *Clostridium perfringens* had the ability to digest healthy muscle tissue. In the 1940s, the enzyme was named collagenase when the culture filtrates were able to digest the collagen framework of healthy Achilles tendon. In DC, the combination of two collagenase enzymes acts to lyse the pathological cords and facilitate rupture with manipulations of the tethered joints. Enzymatic fasciotomy was first used in the treatment of DC by Bassot (Bassot 1965). Hueston repeated the experiment with a mixture of non-CCH including trypsin, hyaluronidase, and lidocaine in 1971 with good results; however, they were short-lived and he abandoned it (Hueston 1971). In 1996, Lawrence Hurst published the first in vitro study of collagenase treatment on surgically excised Dupuytren cords (Starkweather et al. 1996). This was followed closely in 2000s by the first of a series of in vivo studies that would eventually lay the groundwork for the approval of CCH (Badalamente and Hurst 2000; Gilpin et al. 2010; Hurst et al. 2009).

The FDA approval of collagenase clostridium histolyticum (CCH) for the treatment of Dupuytren contracture in the United States in February 2010 marked the first successful non-surgical intervention for DC and the first novel treatment option in nearly two centuries. Its introduction provides an interesting case study for impact of a novel and successful drug on the diagnosis and treatment of a given disease. The purpose of this study is to evaluate the impact CCH had on the awareness of DC by studying the changes in diagnosis trends and the effect it played on the treatment patterns.

4.2 Methods

The IMS (Intercontinental Marketing Services) Health Hospital Procedure/Diagnosis database was analyzed from January 2007 through December 2013 for the diagnoses of Dupuytren contracture (ICD-9-CM 718.44, 728.6) and surgical procedure codes for open surgery (Fasciectomy or Fasciotomy, CPT 26121, 26123, 26125) or needle aponeurotomy (NA, CPT 26040, 26045). The IMS database captures 75 % of all US discharges (including 100 % of Medicare reimbursed discharges).

CCH usage trend 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 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.

4.3 Results

During the study period, there was a steady increase in the number of patients diagnosed with DC per quarter. For example, the number of DC diagnoses in 2007 first quarter compared with that of 2013 first quarter reveals a 38 % increase in the diagnosis of DC (Fig. 4.1).

Since the approval of CCH in Q1 2010, the use of CCH has steadily increased from 5 % of all DC procedures to almost 30 % in 2013 (Fig. 4.2). This coincides with a decrease in the percentage of surgical procedures from about 80 % to about 60 %, while the percentage of NA remained relatively steady at approximately 10 % throughout the study period.

The total monthly DC open procedures followed a seasonal variation with more surgeries in the months of November, December, January, and February (Fig. 4.3). The same seasonality was not observed with closed surgical methods or CCH

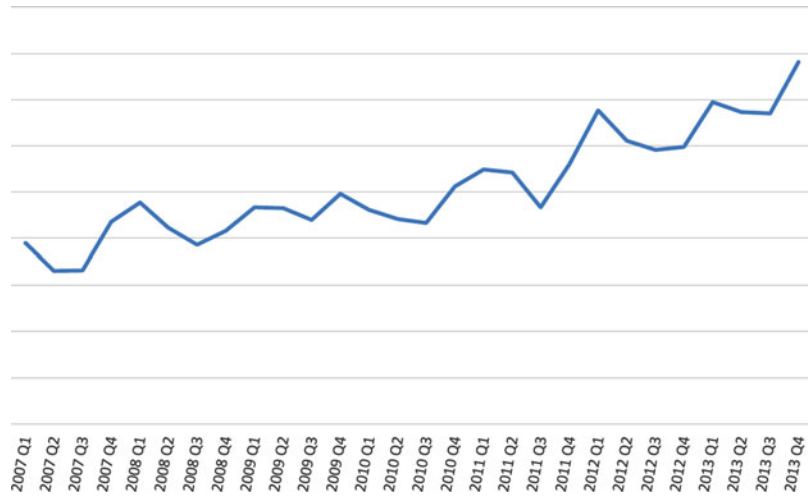

Fig. 4.1 Number of DC diagnoses by quarter

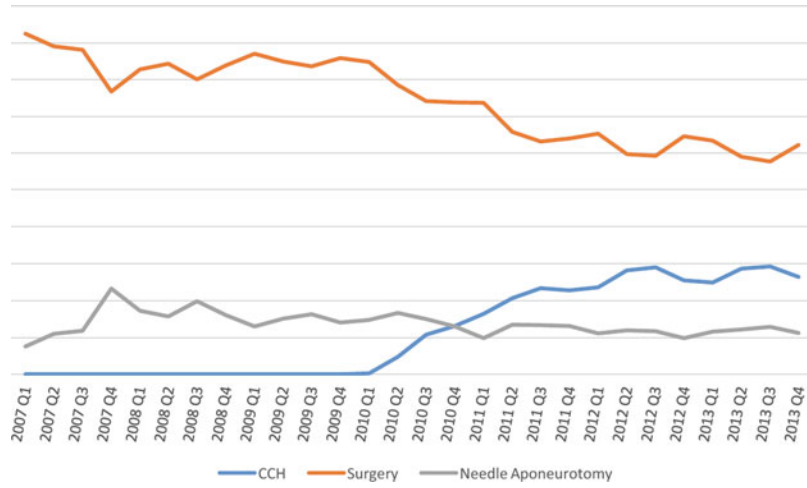

Fig. 4.2 Procedure market share by quarter

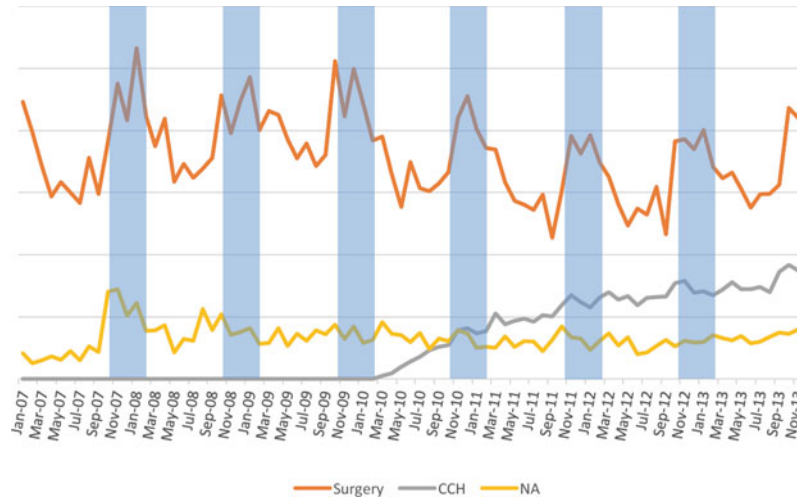

Fig. 4.3 Seasonality of open surgery during the winter months

injections. The variation was not altered after the introduction of CCH in 2010 or the three subsequent years studied.

4.4 Discussion

This study is an interesting case study with regard to pharmaceutical marketing. Although DC is a relatively small disease, Auxilium pharmaceuticals spent $18.2 million in advertising in 2010, placing them at #23 in the top 25 largest pharma advertisement spending of that year (Bulik 2011). The health profession and public were inundated with front-page advertisements in magazines, orthopedic journals, and major exhibits at many national medical conferences.

Not surprisingly, the introduction of CCH into the marketplace in 2010 leads to an increasing trend in the diagnosis of Dupuytren contracture over the next three years. This is likely more a phenomenon of increased awareness of the disease than a true spike in the incidence of DC in the population. We hypothesize that the increased awareness of the disorder and hope for a nonsurgical option led patients to seek medical attention that otherwise would not have.

In the year 2013 in the United States, 42 % of treatment for DC was not open surgery, compared with only 15 % in 2007. In over two centuries, the progress of DC treatment was limited to surgical improvements. CCH provided an alternative treatment that was readily accepted and adopted.

The increased CCH use correlates with the decrease in surgery. It makes sense that there would be a decline in the percentage of open surgical procedures with a novel nonsurgical option. Meanwhile, the number of NA procedures remained steady throughout the study period. The consistency within NA treatment suggests that those practitioners who perform NA were not swayed to CCH, but further research into this is needed.

The number of open surgery cases follows a predictable seasonal variation with more procedures during the winter months while closed NA and CCH injections were consistent throughout the year. This is a unique finding within the Dupuytren surgery population. In a review of the literature, there are no other reported elective hand surgical cases with this seasonal variation. There is not an overall increase in other surgeries during the winter months, and this must represent a preference for DC patients. We surmise that the patients are less likely to undergo surgery during the warm weather months when casts and bandages are less accepted and patients want to use their hands for work and leisure activities.

These preliminary results are a descriptive analysis of US Dupuytren contracture data. Further statistical analyses in the finished study will greatly expand and strengthen the validity of these current observations.

Conflict of Interest Declaration Authors received data from Auxilium Pharmaceuticals (Endo) but received no financial support for this study.

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International Patient Survey (Part 1: Dupuytren Disease)

5

Wolfgang Wach and Gary Manley

Contents

5.1 Introduction

The advent of new, additional treatments for Dupuytren Disease offers more options but also requires more information for choosing the right one. For counseling, physicians need to understand strengths and weaknesses of *all* available therapies and the preferences of patients, individual, and in general. Physicians have already been surveyed across Europe and elsewhere how they are treating Dupuytren Disease and what side effects they are observing (Dahlin et al. 2013; Dias et al. 2013). The aim of this survey is getting more insight into aspects of counseling by physicians, such as completeness of information about the various treatment options and satisfaction of patients with the treatment provided. The authors hope that results of this survey will help to improve understanding of what aspects of counseling are important for patients and will encourage additional studies to further improve treatments. Ultimately it is the patient who decides how beneficial and successful a treatment is.

Part 2 of this survey addressing Ledderhose Disease is presented in Part 9 of this book (Schurer et al. 2016).

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5.2 Materials and Methods

5.2.1 Concept and Goals of the Survey

To reach as many patients as possible, the survey used a simple online questionnaire. The questionnaire was in English, except for Germany and Austria, where an in German translated version was used. Patients started the survey through a SurveyMonkey website. Questions were intended to be easy to understand, without further explanations, and filling out the survey should be possible in 5 min (verified by the authors prior to the survey and confirmed by tracked response times: about 25 % of the respondents took less than 5 min to fill out the survey).

The survey had four sections, the first one covered 12 general questions (e.g., age, gender, family history, other diseases, lifestyle, country), the second one addressed Ledderhose Disease, the third section asked questions about Dupuytren Disease (e.g., how long have you been suffering from it, what treatments did you receive, how do you rate the effectiveness of the received treatment), and the last section asked to rank the experience of the medical community and had two open-ended questions ("Do you feel there is anything that needs to be improved with regard to counseling, available information, treatment options, rehab, research, etc.?" and "Is there any relevant information you would like to provide?"). Patient could choose which questions were applicable for them and responded to those only.

Overall the survey addressed:

- Quality of treatments
- Quality of counseling
- Effect of lifestyle (smoking, drinking)
- Related diseases
- Country-specific differences, if existing
- Needs of patients (open-ended questions).

A few of the questions were redundant to allow checking validity, e.g. it was asked "how old are you", "when did your disease start", and "how long have you been suffering".

The data were collected without patient identification, i.e., without name, address, or email address. Only IP address, country, age, gender, and time of data entry were recorded. Everybody could participate; a clinical diagnosis was not required (being often inconsistent anyway; Anthony et al. 2008), but we presumed that treated patients were properly diagnosed before treatment.

5.2.2 Participating Organizations

The survey was initiated by Gary Manley's Ledderhose Disease blog and then extended to include Dupuytren Disease. Supporting organizations were:

- The Ledderhose Disease blog
- The International Dupuytren Society
- The British Dupuytren's Society
- The German Dupuytren Society (Deutsche Dupuytren-Gesellschaft)
- The Dupuytren Foundation.

Patients were invited to participate in the survey via websites, forums, and mailing lists. In Germany some clinics additionally encouraged their patients to participate. We estimate that *all* together about 10,000 patients were invited. It was not a requirement that patients had been treated already, i.e., the survey includes also patients in the early stage of disease, which is different to most studies researching patients from hospitals or clinics exclusively.

5.2.3 Data Correction

Patients participated in the survey without having to register. We had no protection against misuse, but did not find any indication of misuse either. One problem with not having to register was that patients could fill out the survey more than once. Occasionally and obviously a patient wanting to correct a wrong input started again from scratch instead of going back to the previous page or question. Typically these records were close to each other (similar or subsequent session ID),

used the same IP address, and were identical except very few entries, and the first record was typically only partially filled. In those cases the first record was deleted from the survey (31 records deleted).

The difference between "age" and "In years how long have you had Dupuytren's?" gives the age of onset, which was additionally inquired by "At what age did you first start showing symptoms of Dupuytren's?." If those values differed, the record was inspected. A typical mistake was, e.g., entering something like "2004" as age of onset. This was corrected.

5.2.4 Statistics

Data were stored as spreadsheets; for analysis the English and German spreadsheets were merged into one. Evaluation was by conditioned spreadsheet functions, like AVERAGEIFS. The Kruskal–Wallis test was applied for analyzing the effect of drinking and the Mann–Whitney U test for analyzing the effect of smoking, both by using SPSS.

5.3 Results

Data collection started in July 2014. The survey is still ongoing (http://www.dupuytren-online.info/Forum_English/, accessed September 2015), but the results presented here are based on the data collected until the end of March 2015. The total number of responses for Dupuytren Disease at that time was 2,235; 1,310 male and 925 female patients participated (ratio of 1.4:1). The average age was 59 for both genders. Including patients who suffered from Ledderhose Disease only, the overall response rate of the survey was about 25 %.

Due to the two languages used, participants were mainly from the USA, the UK, and Germany (Fig. 5.1). Larger contributions came also from Canada (94) and Australia (90). Patients did not have to answer *all* questions; therefore for most questions, the number N of responses is less than the total number.

5.3.1 Gender-Dependent Age of Onset

The average age of onset of Dupuytren Disease of *all* patients was 47.7 (median = 49). Figure 5.2 shows the age of onset by age groups and could be interpreted that for men, Dupuytren Disease starts about 10 years earlier than for women (Ross 1999). But that is an artifact caused by the specific age grouping. According to our data, men develop this disease on an average at the age of 46 and women at an age of 50.1, i.e., only 4 years later ($p < 0.001$). Note that earlier onset for men appears even in the lowest age group,

Europe:

Country	DD patients
Austria	15
Belgium	5
Denmark	4
France	14
Germany	**399**
Holland	23
Ireland	28
Norway	3
UK	**367**
Other Europe	38

Fig. 5.1 Geographical distribution of participants with Dupuytren Disease

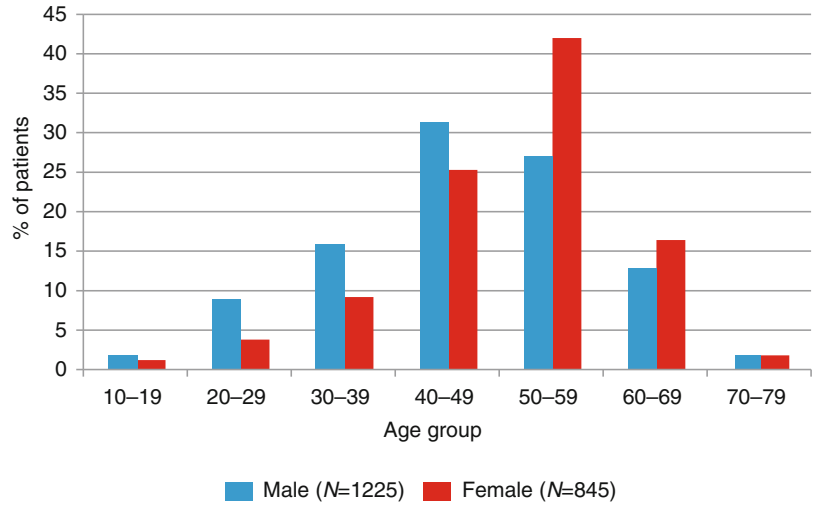

Fig. 5.2 Gender-dependent age of onset of Dupuytren Disease

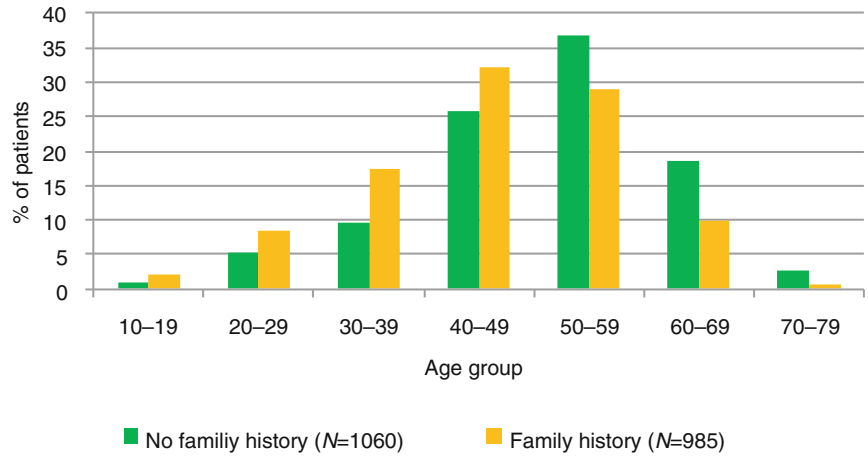

Fig. 5.3 Age of onset with and without family history

where work or lifestyle has no effect yet. Although in that age group statistical significance is low (male $N=21$, 1.7 %; female $N=10$, 1.2 %), it might still indicate genetic causes.

5.3.2 Family History

Family history is also affecting the age of onset. Figure 5.3 shows the data for *all* participants, excluding patients who were not sure.

On average our patients with confirmed family history report an onset of Dupuytren Disease at 44.9 years (median = 45), while those without family history have an average age of onset of 50.3 years (median = 51). For men with family history, we find 42.8 years and 49.4 years without ($p<0.001$), for women 44.9 and 50.3 years, respectively ($p=0.003$).

5.3.3 Lifestyle

To explore the effect of drinking alcohol and smoking, patients were asked whether they were currently smoking or not (smoking: male = 11 %; female = 9 % with higher percentages in Europe and lower in the USA) and whether they were

drinking less than 2 glasses of wine/pints of beer per day, more than 2 glasses or not drink at *all*. We did not inquire about previous habits (Table 5.1)

Figure 5.4a shows the effect of smoking on the age of onset for *all* patients. Figure 5.4b excludes other influences causing an earlier onset, like male gender or family history.

Smoking seems to cause an earlier onset. The effect is most obvious in the age group 30–39 ($N=50$ smoking, 224 not smoking for *all* patients), where people already have smoked for a longer period of time. It seems to take a while until the effect builds up because it is still smaller in the age group 20–29. The effect is similar for both genders: in the age group 30–39 smokers develop Dupuytren Disease twice as often as nonsmokers: 32.4 % of male smokers vs. 16.1 % of male nonsmokers and 20.5 % of female smokers vs. 9 % of the female nonsmokers.

According to our results (Table 5.2; patients with age of onset < 15 are excluded), smoking men develop Dupuytren Disease 7 years earlier if they have no family history, and only 3 years earlier with family history, but unfortunately results for smokers are lacking statistical significance. You have to start with large numbers for such an analysis. Interestingly, for smoking + family history, the age of onset is about 9–10 years earlier for both, men and women.

Different to smoking we did not observe a negative effect of the drinking behavior on the onset of Dupuytren Disease (Table 5.3); *p*-values are varying between 0.12 and 0.77.

Table 5.1 Daily drinking habits of the participants

	Male	%	Female	%	Total	%
I do not drink	252	19.2	325	35.1	577	25.8
Less than 2 glasses	685	52.3	499	54.0	1184	53.0
More than 2 glasses	373	28.5	101	10.9	474	21.2

Table 5.2 Effect of family history, smoking, and gender on the age of onset

Family history	Yes	*N*	No	*N*	*p*-value
Male not smoking	43.5	521	50.4	345	*0.001*
Male smoking	40.7	47	43.3	52	0.838
Female not smoking	48.5	382	53.0	192	*0.001*
Female smoking	43.9	28	45.7	23	0.588

Table 5.3 Effect of alcohol, smoking, and gender on the age of onset

Alcohol	>2 glasses	<2 glasses	Not drinking
Male not smoking	47.9	45.8	45.9
Male smoking	42.6	43.4	39.6
Female not smoking	50.8	50.1	51.0
Female smoking	49.5	44.5	47.0

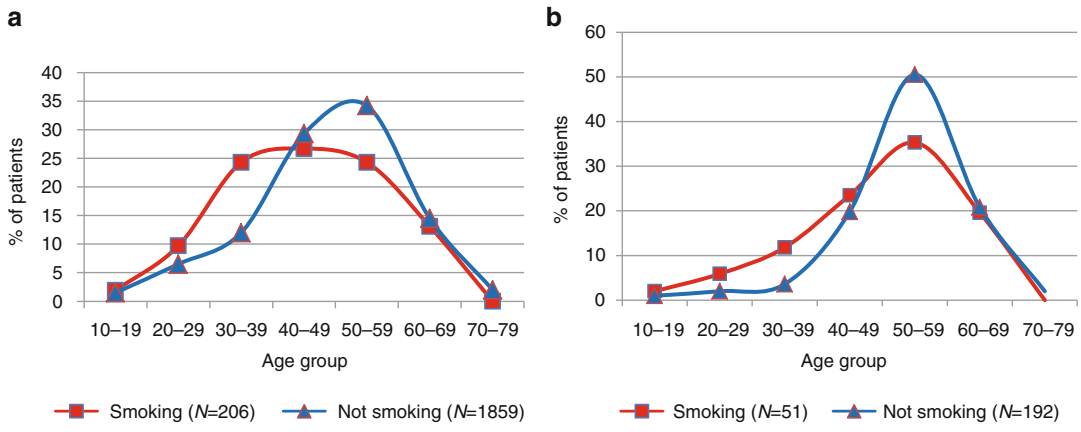

Fig. 5.4 Smoking and age of onset. (**a**) *All* patients. (**b**) Only female patients without family history

Table 5.4 Average age of onset of Dupuytren Disease with and without various comorbidities

Disease	KP	No KP	LD	No LD	LD + KP	No LD/KP	FS	No FS	IPP [a]	No IPP [a]
Average age of onset	40.8	49.1	43.9	49.2	38.8	50.0	47.8	47.6	46.5	45.9
CI (+/–)	1.25	0.55	0.9	0.6	1.65	0.6	1.1	0.6	2.1	0.75
Median	42	50	45	50	40	51	50	49	47	46
P-value	<0.001		<0.001				0.04		n.s.	
N	363	1707	609	1461	193	1291	415	1655	118	1107

KP knuckle pads, *LD* Ledderhose Disease, *FS* Frozen Shoulder, *IPP* Peyronie disease, *n.s.* not significant
[a]Male patients only; confidence interval, 0.95

5.3.4 Related Diseases

93 % of *all* respondents had Dupuytren Disease and 35 % had Ledderhose Disease. Of the patients with Dupuytren Disease, 30 % had Ledderhose Disease, 20 % Frozen Shoulder at least once (Germany alone, 8 %), 17 % knuckle pads, 12 % thyroid problems, and 5 % diabetes. 9.5 % of the male respondents had Peyronie disease. For the 4 most frequent comorbidities, knuckle pads seem to be related to an onset even earlier than Ledderhose Disease, while we find no effect of frozen shoulder or Peyronie disease on the age of onset of DD (Table 5.4). P-values were calculated by linear regression analysis using SPSS.

5.3.5 Patients' Rating of Medical Counseling

Patients were asked "Given your experience to date, how would you rank the medical community's knowledge and experience with Dupuytren Disease?" on a range of 1–10 with 1 = no knowledge, 10 = knew everything. Figure 5.5 shows results by country. For better overview the ratings 1–3 (= bad; red), 4–7 (= medium; yellow), and 8–10 (= good; green) are combined.

Table 5.5 is an attempt to analyze cultural differences, specifically whether English-speaking patients would be more reluctant to express criticism than German ones. Obviously this is not the case (see also Fig. 5.5). The differences might indicate actual difference of knowledge in the medical community. Of course, ratings of countries with very few participants, like Ireland ($N = 21$), may be more skewed by individual experiences.

5.3.6 Patients' Rating of Treatments for Dupuytren Disease

Patients were asked to rate the outcome of treatment(s) of Dupuytren Disease that they had had themselves. Treatments included in the survey were those which we had seen mentioned most in forums. If a treatment received was not listed, patients could select "Other." Each patient could rate more than 1 treatment. The scale was from 1 = made it worse to 10 = very successful (Fig. 5.6).

Verapamil is a topical crème to reduce/break down scarring. It is obviously not a very frequent treatment but was included in the survey because we knew from forums that it was not very successful and we wanted to check whether this is reflecting in this survey. "Other treatments" get a surprisingly good rating but are in detail covering a wide range of treatments (patients could explain those in the comments). Massaging was the most mentioned successful treatment in the "Other" category.

5.3.7 Comments and Suggestions from Patients

The open questions brought an overwhelming response, close to 1,900 suggestions and more than 800 additional comments. The responses often included the patient's personal experience and disease history and quite a few answers covered ¼–½ pages. *All* responses were judged valuable.

Two wishes appeared most frequently: *more research* for finding a cure, finding new treatments, and better understanding and optimizing available treatments (including success chances, hand ther-

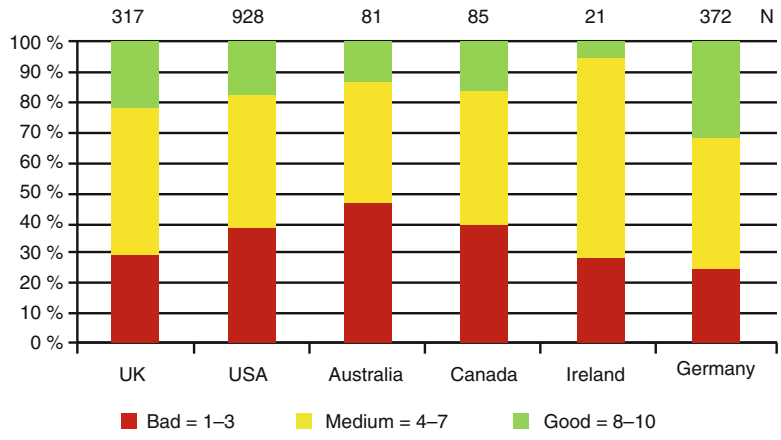

Fig. 5.5 Patients' rating of the medical community's knowledge of Dupuytren Disease by country

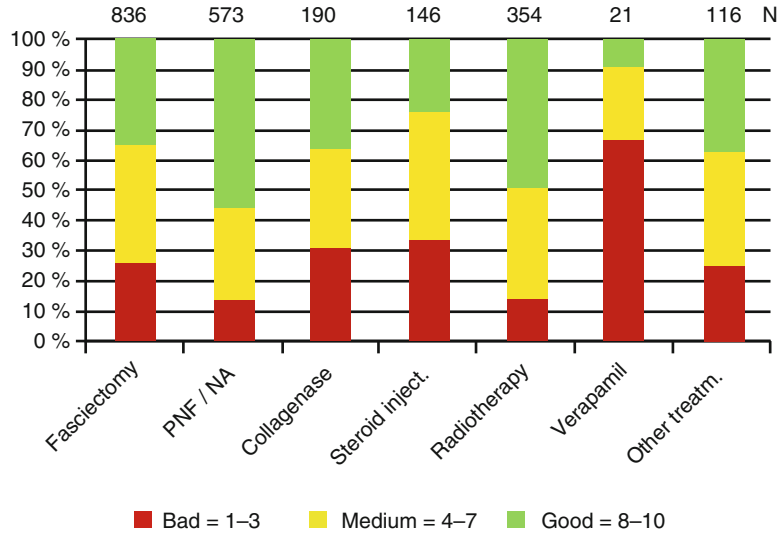

Fig. 5.6 Patients' ratings of treatments of Dupuytren Disease

Table 5.5 Rating of physicians' DD knowledge by German- and English-speaking participants (% patients)

1	2	3	4	5	6	7	8	9	10	Rating
3.8	7.5	13.4	12.1	13.4	6.7	11.6	13.4	7.5	10.5	German ($N=372$)
7.3	13	16.4	10.3	16.9	9.1	9.4	8.1	3.4	6.2	English ($N=1636$)

apy, and reducing side effects). Some comments suggested including research on Peyronie disease, one referring a specific paper (Valente et al. 2003) because the medication (arginine) had very positively affected his Dupuytren Disease.

The other frequent topic was *better education of physicians* to understand *all* treatment options and provide better counseling. Many patients were dissatisfied with the quality of information they had received, also reflecting in the ratings (Fig. 5.5).

Occasionally patients complain that GPs may recognize Dupuytren Disease but are not aware of possibly related diseases like Ledderhose, Peyronie, or Frozen Shoulder.

Quite a few patients had familiarized themselves through the Internet about treatment options but had difficulties finding a medical provider. While surgery seemed to be generally available and surgeons have successfully been made aware of collagenase, a frequent request is making PNF and radiotherapy more available.

Comments from Patients

Quality of counseling: "The information on treatment options needs to be shared more, i.e. get it into orthopedic training"; "I believe that hand surgeons or diagnosticians should be held accountable if they do not advise patients about *all* the available treatments"; "I had a ray amputation on my little finger which could have been prevented if I had been referred earlier. I took advice from my GP and feel badly let down"; "Misdiagnosis: 'We won't know what it is unless we cut it open and remove it'. And that operation caused a flare up of nodules"; "The hand surgeon said later that he didn't recognize it as Dupuytrens. Cutting into the bump with the idea of removing it started the disease to advance quickly".

Documentation: "I believe that follow-up data needs to be collated and analysed for presentation to District Health Boards, insurers and other funding organisations to enable fact-based decision making in the context of DD, the lifetime cost of treatment and the quest for the most positive health outcomes."

Massaging as treatment: "I had started forming a habit of massaging it daily. I still massage it every day and it has basically not returned"; "I started applying frequent friction to my Dupuytren's hands by rubbing my thumb back and forth over it and after about a month it started to reduce in size. I have noticed about an 80 % improvement doing this."

Pathogenesis: "Over the past few years I have started to get the feeling that DD/LD have a genetic and an environmental trigger. The genetic seems to occur younger and is more aggressive, while the environmental trigger seems to be more local and less aggressive. Environment triggers could be alcohol, diabetes, hand injury or maybe just old age. Could this be so and if it is, should the treatment options be different?"

Improvement of this survey: "more options for fill in responses, more guidance for questions that have a 1–10 rating scale, or better yet replacing a single question scale by a collection of sub-questions that would lead you to better overall data and understanding. I do not think that anyone taking this survey would be put off at *all* by having to answering a much longer and more detailed questionnaire"; "given the length of presence of the disease, i do not think the questions adequately gave a true picture … the complications of tendon issues, nerve damage, arthritis in the progression of the disease were not addressed"; "I do think your survey could have been better served with a question rating the affliction's impact on quality of life"; "I think that *all* the information about this disease should be gathered in one big database".

Patients emphasize that DD can be quite painful. Improved listening skills of the physicians were requested several times. Regular and frequent massaging seems to be beneficial for some patients.

5.4 Discussion

This survey was conducted to assess the quality of counseling and treatment as perceived by patients with Dupuytren Disease and to better

understand what patients need and are missing. Additionally, the effect of drinking, smoking, and family history, as well as comorbidities, should be evaluated. To our knowledge this survey is one of the largest surveys of DD patients that has been conducted so far, and it is the first survey with patients rating therapies.

5.4.1 Ratings of Counseling and Therapies

Ratings of consultation and of treatments inquired through an anonymous questionnaire are likely more honest than if patients are interviewed by their treating doctor. We consider these ratings as a key element of our survey.

The ratings of the knowledge of the medical community are generally disappointing (Fig. 5.5). One would hope and thrive for > 50 % good ratings but no country is achieving this (potential biases see Sect. 5.4.3). The UK and Germany are doing relatively well but *all* countries exhibit room for improvement. The specifically bad rating for Ireland is statistically not very relevant. The knowledge of therapies and their side effects might be an area that – in part yet to be established – Dupuytren Societies could gradually improve.

The ratings of therapies (Fig. 5.6) show about equal ratings for fasciectomy, PNF, and collagenase injection. PNF is leading but might be influenced by the possibly positive US bias as discussed below in paragraph 5.4.3. Collagenase and fasciectomy are very similar. Obviously *all* three treatments have their place and have – in the patients' view – good as well as not so good outcomes. There is still room for improvement for *all* therapies according to patients' comments. Bad experience with surgery included pain, slow recovery combined with long hand therapy, disease extension, and damage to the hand. PNF seems to be well tolerated; dissatisfaction focused mainly on quick recurrence (several patients mention that they ended up having surgery). Collagenase injection was criticized for swelling and pain, recurrence, and price. Further surveys investigating into details of negative and positive ratings might help finding improvements for each treatment.

Ratings from patients may differ from ratings from surgeons. Dias et al. (2013) found for Europe "overall, 97 % of the procedures were rated by the surgeon as having a positive outcome" while about 25 % of the patients of our survey are rating the results of fasciectomy as bad. Obviously criteria are different, emphasizing the importance of understanding expectations and needs of patients prior to treatment (Carboni et al. 2015). Our results are matching better with those of Dias and Braybrooke (2006), who interviewed 1,177 British patients after surgery and report that 10 % had no improvement and another 9 % considered their deformity worse after surgery.

By far the best rating is for radiotherapy, confirming its role as treatment for the early stage of Dupuytren Disease, prior to contracture. Negative comments referred mainly to inefficiency in stopping the disease and in some cases to burning sensation and inflammation.

5.4.2 Comparison with Other Surveys

So far only few studies surveyed more than 1,000 DD patients (Dias and Braybrooke 2006 ($N = 1{,}177$), Loos et al. 2007 ($N = 2{,}919$), Anthony et al. 2008 ($N = 1{,}815$), Dahlin et al. 2013 ($N = 3{,}357$) together with Dias et al. 2013 ($N = 3{,}357$), Eaton 2016a ($N = 3{,}120$)). Most of them analyzed patient charts retrospectively; only Dias and Braybrooke surveyed DD patients directly (after they had surgery).

In our survey we have a male/female ratio of 1.4, which coincides with results of Lanting et al. (2013), who did a systematic epidemiology of the Dutch population. This is far less than the ratio of 3.4 observed by Mikkelsen (1972) in Norway. Anthony et al. (2008) find in Boston, USA, in hospitals a gender ratio of 1.7. Other hospital-based ratios are in part much higher, up to 10 (Mikkelsen 1972; Loos et al. 2007). Our average age of 59 is lower than the 62 of Lanting et al. but our data set includes young patients, while Lanting et al. researched only patients of 50 years or older.

Dolmans and Hennies (2012) reported the age of onset in 1,000 Dutch Dupuytren patients

undergoing surgery. While their results qualitatively agree with ours, they are seeing more patients with a later onset. They find that the onset for female patients is peaking in the age group 50–59 (D&H: 34 %; this survey 42 %) but they find still high percentages in the 60–69 age group (D&H: 26 %; this survey 16 %). This sharper drop-off of our data confirms that our survey covered a younger population. While we find an average age of onset of 46/50.1 (m/f), Dolmans and Hennies report an average age of first surgery of 58/61 (m/f), interestingly about the same time difference.

Becker et al. (2014) interviewed patients undergoing fasciectomy or PNF at several German and Swiss hospitals and clinics. They found that positive family history correlates with disease in both hands, recurrence, knuckle pads, and Ledderhose Disease. They do not report a strong effect of alcohol or smoking, in agreement with Loos et al. (2007). While only 5 % of our patients report having diabetes, Becker at al. are finding 14.5 %, Dahlin et al. (2013) in Europe an average of 28 %, and Descatha et al. (2014) 16.7 % in the French GAZEL study (999 patients; average age 68 for men, 65 for women). In a more detailed analysis, Lanting et al. (2013) report diabetes in Dutch Dupuytren patients in the age group 50–55 at 3.7 % and in the age group 56–65 at 11.6 %, demonstrating strong age dependence. The 5 % diabetes that we find at an average age of 59 is approximately matching with the data of Lanting et al. and the slightly older patients set (average age 61.6, 7 % diabetes) of Seegenschmiedt et al. (2012).

Originally the authors had planned comparing percentages of comorbidities with the normal population, but the span of reported "normal" percentages, as discussed above for diabetes, the country dependence, and gender and age dependence are aggravating comparison. For Peyronie disease a prevalence of 0.5–13 % has been reported for the male US population, depending on definition (DiBenedetti et al. 2011), making it difficult to decide whether the 9.5 % found in this survey are just normal. Our observation that having knuckle pads is related to an earlier onset of DD, Ledderhose Disease somewhat less but still measurable, and Peyronie disease having very little or no effect are in agreement with genetic research on diathesis (Dolmans et al. 2012).

Descatha et al. (2014) found a dose relationship of drinking with Dupuytren Disease (affecting prevalence). One reason why we don't observe any effect on the age of onset may be the differently scaled question: Descatha et al. asked for <3 glasses/day, 3–4 glasses/day, and ≥ 5 glasses of wine/beer or ≥ 3 glasses of spirits per day. In the Descatha (GAZEL) study, only 20.8 % are in the lowest category (<3 glasses), while at least 70 % our patients would fall into that category (Table 5.1), which might indicate more heavy drinkers in the GAZEL sample but also problems in self-reporting of drinking habits. Lanting et al. (2013) find a clear effect of alcohol consumption on the prevalence already at about 2 glasses/day.

Eaton (2016a) finds that the percentage of Dupuytren patients also suffering from Ledderhose is clearly related to the age of onset of Dupuytren Disease. This is in remarkable agreement with our data (Fig. 5.7a).

To test whether our data are influenced by an overlap with data from Eaton, a subset of our data (German and British patients only = D + UK in Fig. 5.7a) is also shown, confirming this trend. A possible explanation would be that the age distribution of LD falls off more sharply than for DD but this does not seem to be the case (Fig. 5.8).

Another explanation could be that having both, Dupuytren and Ledderhose Disease, indicates stronger diathesis, while developing Dupuytren Disease late is indication of weak diathesis. Yet this would apply for both, Fig. 5.7a, b and cannot explain the difference. Dolmans et al. (2012) found only a weak link between genetic risk for Dupuytren Disease and Ledderhose Disease. The relation between both diseases deserves further investigation.

5.4.3 Potential Bias and Errors

Participants have not been randomly included in the survey but were invited through mailing lists, websites, and forums. For example, the mailing list of the Dupuytren Foundation might include a relatively high percentage of PNF-treated patients because it includes many former US

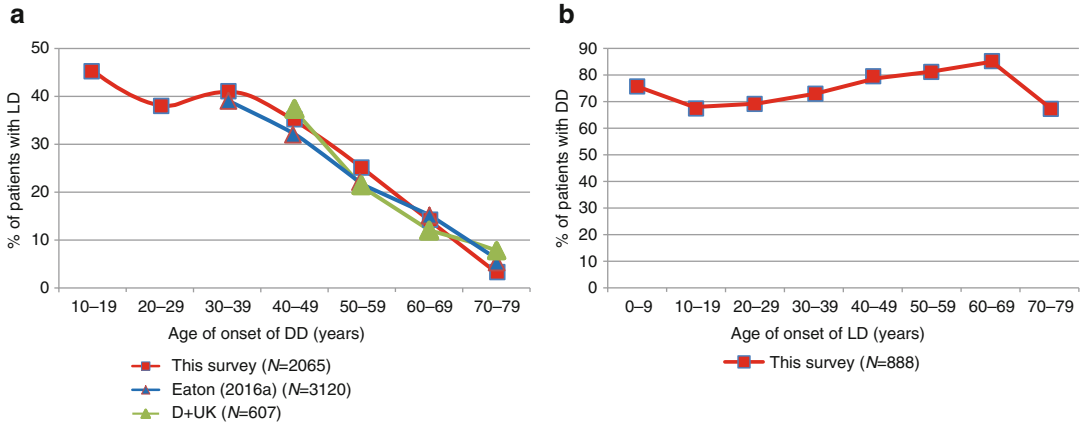

Fig. 5.7 Percentages of patients suffering from DD and LD. (**a**) Percentage suffering from Ledderhose Disease vs. age of onset of Dupuytren Disease. (**b**) Percentage suffering from Dupuytren Disease vs. age of onset of Ledderhose Disease

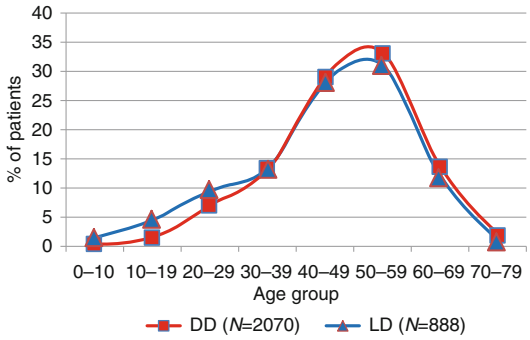

Fig. 5.8 Age of onset of DD and LD

Table 5.6 Average patient ratings of PNF, surgery, and radiotherapy in three countries

Country	USA	UK	Germany
PNF	7.6	5.9	6.4
Surgery	5.9	5.3	5.4
Radiotherapy	7.3	6.8	6.1

patients of Dr. Charles Eaton and those might be more satisfied with PNF than patients from elsewhere, indicated by comments like "I give *ALL* 10 stars to Dr. Charles Eaton who did an amazing NA on my very warped hands" or "… he was god sent."

To check this, we compared ratings of PNF, surgery, and radiotherapy by country (Table 5.6).

Obviously patients from the USA were generally giving better ratings, maybe indicating a cultural difference. This effect is specifically pronounced for PNF, supporting the suspicion of a slight and positive bias of our data regarding PNF in the USA. Of course, the different ratings might also in part reflect different qualities of treatment in those countries.

Bias might also be created in the data because patients visiting forums might be doing this because they had been dissatisfied with their previous treatment. Satisfied patients are more likely to not do anything. So we might have a general bias toward worse ratings. That also applies to ratings of the medical community. Specifically patients dissatisfied with the consultation received may have started educating themselves on the Internet and by doing so ended up on our websites.

Another bias might be induced by using the Internet for this survey, for invitations as well as filling it out. We are more likely covering the younger part of the Dupuytren patients. The average age of our participants is 59. Yet the average onset of the disease is 48 meaning that on an average, our participants have had about 10 years of experience with Dupuytren Disease. We do not expect that a slightly lower age of the participants has affected ratings.

Although we had no complaints about the questionnaire being too complicated, using an online, not assisted, self-reporting instead of medical records may be subject to misunderstandings, entry errors, and recall errors.

Conclusions

- For patients it is important to find a doctor who is able to inform them about *all* treatment options and to provide good counseling which treatment is optimal for the patient's specific situation; for doctors it is important to understand the patient's personal preferences.
- None of the established treatments of Dupuytren Disease receives overall good ratings from patients. Further research is required comparing treatments and to understand and improve specific shortcomings. Additionally, PNF and radiotherapy are lacking availability in some countries.
- Smoking and family history cause earlier onset of Dupuytren Disease. We don't see an effect of moderate drinking on the age of onset (heavy drinking and prevalence were not analyzed).
- Online surveys offer an easy and versatile means for evaluating patients' perceptions. The disadvantage of online surveys is that there is no control of the quality of input and no possibility to contact the patient in case of further questions. Building a Dupuytren database including patient contact data would help (Eaton 2016b).

Acknowledgments and Conflict of Interest Declaration The authors wish to thank all patients who participated in this survey. The support of participating organizations and several German clinics in inviting patients to this survey is gratefully acknowledged. Statistical analysis with SPSS was performed by CRO Kottmann, Germany. The authors have no conflict of interest to declare.

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Part II

Cellular and Extra-cellular Events, Pathogenesis

David O'Gorman and Boris Hinz,
supported by Charles Eaton

The Extracellular Matrix in Dupuytren Disease

6

David B. O'Gorman

Contents

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6.1 The Pathogenesis of Dupuytren Disease

The pathogenesis of Dupuytren Disease remains controversial and poorly understood. This complex condition resembles abnormal wound repair, a process that can be used to provide a contextual framework for understanding Dupuytren Disease development. When normal palmar fascia is wounded, complex arrays of wound healing responses are initiated in local and circulating macrophages, fibroblasts, and other cells that contribute to tissue homeostasis. Under ideal conditions, the signaling pathways that are transiently activated in these cells promote high-fidelity repair that superficially resembles palmar fascia regeneration. Unfortunately, palmar fascia repair also occurs under suboptimal conditions such as chronic microtraumas (Mikkelsen 1978; Liss and Stock 1996), excessive inflammation (Baird et al. 1993; Qureshi et al. 2001; Gudmundsson et al. 1998), and abnormal metabolic (Savas et al. 2007) and/or biomechanical (Verhoekx et al. 2012) stimuli from the extracellular environment. While these conditions alone are often sufficient to modify cellular responses and reduce the quality of subsequent repair processes, their impacts may be amplified when these cells carry heritable, pro-fibrotic genomic traits (Dolmans et al. 2011; Debniak et al. 2013; Bayat et al. 2002). These heritable traits are hypothesized to modify cellular sensitivities to

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adverse conditions and induce chronic activation of signaling pathways that are transiently activated during normal palmar fascia repair and the activation of additional signaling pathways that are normally restricted to development rather than repair (Rehman et al. 2008). The net result is the excessive secretion of collagens (Badalamente and Hurst 1999) and other extracellular matrix molecules by hyper-contractile tissue repair cells known as the myofibroblasts (Tomasek et al. 1999; Vi et al. 2009a). These cells, which have transient but essential roles in normal tissue repair, constantly remodel and contract the collagen-rich matrix they secrete, thereby increasing tissue density and ultimately causing palmar fascia contractures (Meek et al. 1999).

When viewed from this perspective, it is apparent that abnormal environmental stimuli and heritable genomic (genetic and epigenetic) factors act in combination to cause Dupuytren Disease. Ideally, therapeutic interventions to prevent Dupuytren Disease development would target both of these contributing factors simultaneously. Unfortunately, the complex genomic traits that are hypothesized to modify cellular sensitivities to adverse microenvironments and predispose individuals to develop Dupuytren Disease are yet to be clearly defined. Even when they are defined, we may have to await the development of reliable, safe, and approved genome-editing tools before it is feasible to intervene and correct them. However, some of the abnormal environmental stimuli that promote Dupuytren Disease are amenable to therapeutic interventions and are already being targeted in other disease systems. For example, pharmacological inhibitors of some of the inflammatory cytokines hypothesized to induce Dupuytren Disease development, such as TNFα (Verjee et al. 2013), are currently being used to treat inflammatory arthritis (Meroni et al. 2015; Bader and Wagoner 2011). However, to develop effective therapeutic interventions that target these cytokines or other molecules that promote Dupuytren Disease progression and recurrence, we must first take into account the unique palmar fascia microenvironment within which these interventions must take place. This microenvironment consists of a mixture of resident palmar fascia, immune and other cell types embedded in extracellular matrix (ECM) that is unique to this tissue. The central hypotheses of this section are that the ECM in the palmar fascia of patients with Dupuytren Disease is not normal, that it influences disease progression and recurrence, and that it is a viable and readily accessible target for therapeutic interventions to prevent Dupuytren Disease. Before we can determine whether or not the available evidence supports these hypotheses, we must first understand the cellular origins of the Dupuytren Disease ECM, its complexity, and how it interacts with contracture-causing cells.

6.2 The Cellular Origin of the Extracellular Matrix in Dupuytren Disease

The ECM can be described as a complex mixture of proteins and other molecules secreted by cells to provide structural support within a three-dimensional tissue. While this description is accurate, it omits what is arguably the most important role of the ECM, to provide the biochemical and biomechanical feedback that cells require to "sense" their local environment (Aszódi et al. 2006; Piccolo et al. 2014). Dupuytren Disease, like many other fibroses, is characterized by excessive ECM secretion and remodeling. The cells that secrete, condition, and contract the ECM in Dupuytren Disease are hyper-contractile connective tissue myofibroblasts. While circulating and resident macrophages, progenitor/stem, and other cells may play important roles in initiating fibrosis, the substantial overlap between the gene expression profiles of Dupuytren Disease-derived myofibroblasts and of palmar fascia fibroblasts in the adjacent, non-fibrotic palmar fascia strongly suggests that the majority of ECM-secreting myofibroblasts in contracture tissues are derived from the palmar fascia (Satish et al. 2008, 2012). Comparisons between myofibroblasts derived from Dupuytren Disease tissues and fibroblasts derived from normal carpal ligament have revealed

that Dupuytren Disease myofibroblasts not only secrete excessive quantities of ECM, but they also achieve "tensional homeostasis" with their ECM at much higher contractile forces (Bisson et al. 2004). These findings suggest that Dupuytren Disease myofibroblasts either have an impaired ability to recognize normal levels of tensional feedback from their ECM or that the biochemical and biomechanical signals that these cells receive from this ECM actively promote their excessive contractility. There is evidence to support the latter interpretation and, by extension, the hypothesis that the Dupuytren Disease ECM itself promotes disease progression.

6.3 The Complexity of the Extracellular Matrix in Dupuytren Disease

The ECM in Dupuytren Disease is very complex and, as yet, poorly defined. It contains hydroscopic carbohydrate polymers that act in combination with ECM proteins and act as proteoglycans, such as chondroitin sulfate (Bazin et al. 1980; Slack et al. 1982; Flint et al. 1982), and others that act independently of proteins, such as hyaluronan (or hyaluronic acid) (Slack et al. 1982; Andreutti et al. 1999). While ECM proteins are typically divided into structural and nonstructural categories, there is considerable overlap between these categories. For example, the most abundant proteins in contracture cords are type I and type III collagens (Bailey et al. 1977; Brickley-Parsons et al. 1981; Bunker et al. 2000). While their central roles in providing structural integrity to cords are beyond dispute, these proteins also function as signaling molecules (Imamichi and Menke 2007) that induce a variety of cellular responses (Vi et al. 2009b) through well-established cell surface receptors (Naci et al. 2015). Other Dupuytren Disease-associated ECM proteins with structural and signaling roles include other collagens (Magro et al. 1997a), laminin (Tomasek et al. 1986; Magro et al. 1997b; Tomasek et al. 1987), elastin (Neumuller et al. 1994), and insoluble fibronectin, including the alternatively spliced form of fibronectin known as extra domain A (EDA) or "oncofetal" fibronectin (Kosmehl et al. 1995; Berndt et al. 1995; Howard et al. 2004). Nonstructural "matricellular" proteins that interact with structural ECM proteins and regulate growth factor signaling, such as periostin (Vi et al. 2009a; Shih et al. 2009), tenascin C (Shih et al. 2009), CCN2 (connective tissue growth factor) (Satish et al. 2011), and others, are also abundant in the Dupuytren Disease ECM. ECM metalloproteinase (MMP) levels, tissue inhibitors of metalloproteinases (TIMPs), and activities differ between diseased and visibly unaffected palmar fascia, and these differences are likely to contribute to the imbalance in ECM production and degradation in contracture tissues (Verhoekx et al. 2012; Forrester et al. 2013; Tarlton et al. 1998; Johnston et al. 2007; Bunker et al. 2000). Finally, many growth and differentiation factors are associated with the Dupuytren Disease ECM. Some, such as transforming growth factor β (TGFβ) (Kloen et al. 1995; Badalamente et al. 1996; Berndt et al. 1995), bind the ECM in a latent form and can be activated by proteases in the ECM and also by the biomechanical influences imposed by abnormal ECM stiffness/density (Hinz 2009; Wipff et al. 2007). Others, such as basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and insulin-like growth factor-II (IGF-II) (Gonzalez et al. 1992; Raykha et al. 2013; Badalamente and Hurst 1999; Berndt et al. 1995), either bind the ECM directly as active molecules or are bound indirectly through other proteins with the capacity to bind structural components of the ECM. Genes encoding ECM proteins consistently make up the majority of the dysregulated genes identified in gene expression studies of Dupuytren Disease myofibroblasts and tissues (Rehman et al. 2008; Forrester et al. 2013; Qian et al. 2004; Satish et al. 2012), reflecting the extent of ECM remodeling that takes place during Dupuytren Disease development. We do not understand the functions or therapeutic potential of the vast majority of these molecules.

Examples of molecules previously identified in the Dupuytren Disease extracellular matrix		
Structural and nonstructural ECM molecules	Matricellular (nonstructural) ECM molecules	Growth and differentiation factors
Collagens (I, III, + many others) Decorin Vitronectin Hyaluronan (hyaluronic acid) Proteases (MMP/ADAM/ADAMTS) Protease inhibitors (TIMPs) Laminin Elastin Fibronectin (including EDA)	Periostin Tenascin C CCN2 (CTGF) CCN4 (WISP1)	Transforming growth factor ß (TGFß) Tumor necrosis factor α (TNFα) Basic fibroblast growth factor (bFGF) Platelet-derived growth factor (PDGF) Insulin-like growth factor-II (IGF-II)

6.4 Cellular Connections with the Extracellular Matrix

Connective tissue fibroblasts in general, and myofibroblasts in particular, obtain feedback from the biochemical and biomechanical components of their ECM (Hinz 2006; Tomasek et al. 2002) through specialized attachment points known as focal adhesions. While several different types of attachments have been characterized in *in vitro* settings, including focal complexes, fibrillar adhesions, and 3D matrix adhesions (Berrier and Yamada 2007; Harunaga and Yamada 2011), the primary cellular attachments that are formed *in vivo* are focal adhesions (Lock et al. 2008; Christopher and Guan 2000; Hinz et al. 2003) (Fig. 6.1). Focal adhesions are dynamically regulated multi-protein complexes of integrins and other proteins that span the cell membrane and connect cells to proteins in the Dupuytren Disease ECM, which include collagens (Magro et al. 1997a), laminin (Wilbrand et al. 2003), fibronectin (Magro et al. 1995), and matricellular molecules (Vi et al. 2009a). Both biochemical and biomechanical stimuli can activate focal adhesions to facilitate cellular responses. Many of these responses involve the polymerization of globular (G) actin monomers into the filamentous actins (F actin). Actin filaments bind vinculin and other focal adhesion proteins (Hinz and Gabbiani 2003a) to complete the structural link between the ECM and the cytoskeleton and facilitate ECM-induced changes in cellular motility, contractility, and substrate adhesion (Kawaguchi et al. 2003; Yamashiro et al. 1998; Hinz and Gabbiani 2003a).

6.5 Cellular Tensegrity Within the Extracellular Matrix

Myofibroblasts can be distinguished from other fibroblasts by their expression of a distinct form of filamentous actin known as α smooth muscle actin (αSMA) (Darby et al. 1990). When coupled to myosin in "stress" fibers, αSMA allows myofibroblasts to impose much greater contractile forces on the ECM through focal adhesions than connective tissue fibroblasts are normally capable of achieving (Hinz 2006). Myofibroblasts can also form intercellular (cell to cell) connections with other myofibroblasts through adherens junctions, further enhancing their capacity to coordinate ECM contraction in areas of high cell density (Follonier et al. 2008; Hinz and Gabbiani 2003b).

One way of visualizing cellular interactions with their surrounding matrix is to perceive cells as prestressed lattice structures that are stabilized by the combination of tension and compression. This concept, known as the tensegrity principle (Ingber et al. 2014), envisages actin/myosin stress fibers, intermediate filaments, and microtubules (α and β tubulin polymers) as tensional and compression elements that have analogous roles to the cables and columns that maintain the shape of a flexible structure. While a detailed description of cellular tensegrity is beyond the scope of this section (for details, see (Ingber et al. 2014)), it is nonetheless helpful for envisaging how external forces that pull on structural molecules in the ECM can cause integrins in focal adhesions linked to αSMA in stress fibers to distort the shape of a cell and stimulate cellular responses. This concept

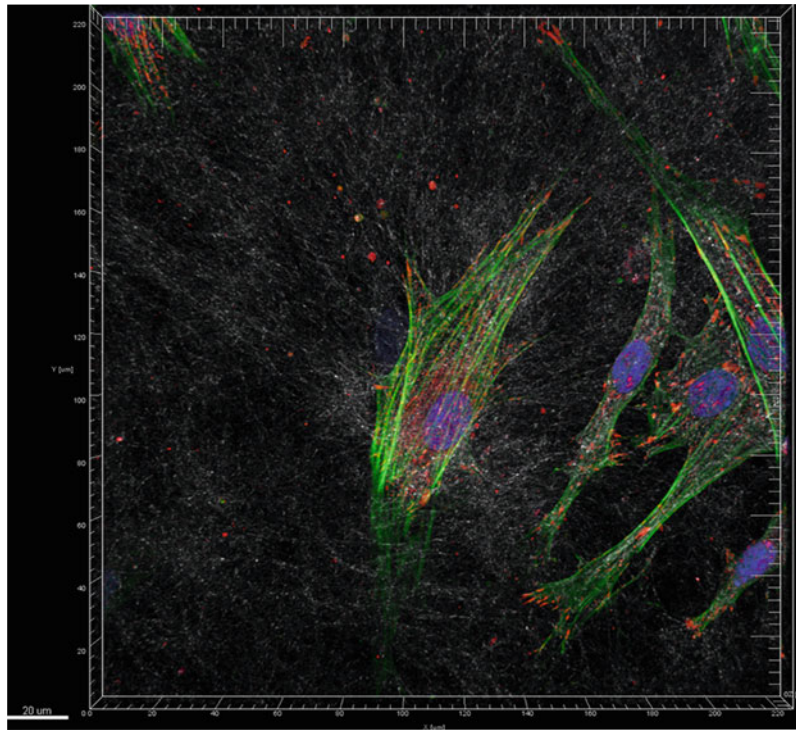

Fig. 6.1 Three-dimensional confocal microscopy of Dupuytren Disease myofibroblasts cultured in type 1 collagen lattices. Stress fibers are stained with green Alexa 488 phalloidin, focal adhesions (vinculin immunoreactivity) are shown in red, and cell nuclei (DAPI staining) are shown in *blue*. The three-dimensional collagen matrix was visualized by laser reflectance microscopy, a technique that utilizes the reflection of laser light by the surfaces of collagen fibers (*white*). Changes in fluorescence intensity within and around these cells indicate cellular processes that are in or out of frame in this two-dimensional rendering of a three-dimensional image. These images illustrate the connections between matrix-associated collagen fibers, focal adhesions, and contractile stress fibers in myofibroblasts. Cells can be envisaged as prestressed lattice structures that are stabilized by the combination of tension and compression in accordance with the tensegrity principle (Ingber et al. 2014). Changes in stress fiber length within cells are translated through focal adhesions to impose changes in collagen fiber density

also works in reverse, allowing cells to contract the surrounding ECM by shortening the actin/myosin stress fibers in their cytoskeleton that are linked to integrins in focal adhesions and to structural molecules, such as collagens, in the ECM.

6.6 Extracellular Matrix Interactions and *In Vitro* Analyses of Dupuytren Disease Cells

Any molecule that promotes the coordinated and excessive contracture of the palmar fascia by myofibroblasts has potential as a therapeutic target. While many of these molecules may reside within palmar fascia fibroblasts or myofibroblasts, others elicit their signals through matricellular and other molecules to induce their effects through focal adhesions to modify cellular proliferation, myofibroblast formation, ECM secretion, or other disease-associated changes. For this reason, *in vitro* studies are performed on palmar fascia fibroblasts or fibrogenic myofibroblasts that do not include a physiologically relevant ECM risk, omitting the contributions of these interactions and, at worst, providing misleading information about cellular responses to treatments.

In practice, culturing cells in a physiologically relevant ECM is technically challenging, especially when most of the constituents of that ECM are yet to be characterized, as is the case in Dupuytren

Disease. One approach to partially overcoming this hurdle is to collect the secretions of primary palmar fascia myofibroblasts and use them to "condition" collagen, hydrogel, or other relatively porous substrates in which cells can be cultured in three dimensions. While this approach can only provide an approximation of an ECM that is continually modified *in vivo,* nonetheless it has advantages over standard tissue culture plastic (TCP) cultures that include little or no ECM components. In addition to providing an increased capacity to bind and act as a reservoir for secreted proteins and other molecules, these substrates can also be designed to have a stress-to-strain ratio, or Young's modulus, that approximates the "stiffness" of normal or fibrotic palmar fascia. The Young's modulus of normal palmar fascia is lower than most tendons (Millesi et al. 1995) and approximates that of the dermis (10–1,000 Pa) (Hinz 2010; Yeung et al. 2005). Fibroblasts begin incorporating αSMA into their stress fibers, indicating their transition from fibroblasts to myofibroblasts, when ECM stiffness approaches 16,000–20,000 Pa (Hinz 2010). Tissues need to achieve a stiffness range of 25,000–50,000 Pa to maintain myofibroblasts in their hyper-contractile state (Hinz 2009). Interestingly, fibroblasts and myofibroblasts can respond to localized changes in the stiffness in their surroundings by migrating toward areas of increased stiffness through a process called durotaxis (Lo et al. 2000; Lange and Fabry 2013). Whether durotaxis contributes to the increased numbers of myofibroblasts in nodules or contracture cords is currently unknown.

TCP has a stiffness of at least 1,000,000,000 Pa (>1 gPa) (Achterberg et al. 2014), which is several orders of magnitude greater than the stiffness of any fibrotic tissue that fibroblasts or myofibroblasts could ever encounter *in vivo.* Under these conditions, fibroblasts spontaneously and robustly transition into αSMA-positive myofibroblasts without the need for any additional treatment interventions (Hinz et al. 2001). While there are applications where comparisons between uniform cultures of myofibroblasts are useful, it should nonetheless be appreciated that the behaviors or responses of cells under these conditions might have little or no similarity to their behaviors or responses on the substrates they normally interact with *in vivo*.

6.7 Interactions Between the Wnt/ß-Catenin Signaling Pathway and the Extracellular Matrix

This point can be illustrated by observing the interactions between Dupuytren Disease fibroblasts and myofibroblasts, cell culture substrates, and the Wnt/ß-catenin signaling pathway. Wnt signaling regulates ß-catenin levels during embryonic development and in a variety of diseases characterized by excessive cellular proliferation (Thompson and Monga 2007; Bowley et al. 2007; Manolagas and Almeida 2007). In the absence of Wnt signaling, ß-catenin is constitutively phosphorylated by casein kinase 1 and glycogen synthase kinase 3ß (GSK3ß), incorporated into a "destruction complex" that includes adenomatous polyposis coli (APC) and axin and degraded through the 26S proteasome (Bowley et al. 2007; Lam and Gottardi 2011). Wnt signaling induces the phosphorylation and inactivation of GSK3ß, thereby allowing ß-catenin to escape the destruction complex, accumulate in the cytoplasm, and translocate to the nucleus. Once in the nucleus, ß-catenin can bind transcription factors and act as a trans-activating factor to regulate gene expression (Bowley et al. 2007) (illustrated in Fig. 6.2).

The discovery of increased levels of ß-catenin in Dupuytren Disease tissues and in primary fibroblasts derived from these tissues (Varallo et al. 2003; Howard et al. 2003) led to the hypothesis that the Wnt/ß-catenin signaling pathway contributed to the pathogenesis of Dupuytren Disease. This hypothesis received indirect support when genome-wide association studies of patients with Dupuytren Disease identified single nucleotide polymorphisms (SNPs) in loci containing genes that encode Wnts or Wnt signaling-associated proteins (Dolmans et al. 2011). These findings led to a more detailed version of the original hypothesis that heritable abnormalities in Wnt gene expression result in dysregulated

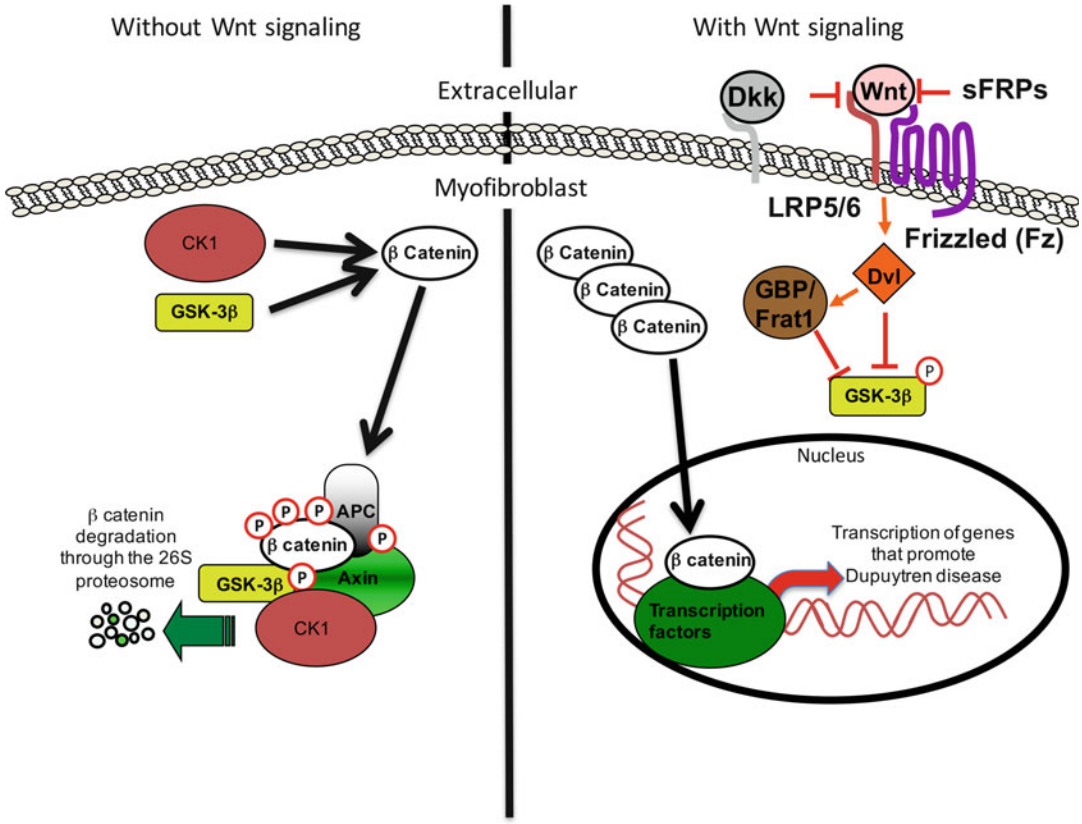

Fig. 6.2 Wnt signaling regulates β-catenin levels. In the absence of wnt signaling (*left*), casein kinase 1 (*CK1*) and glycogen synthase kinase-3β (*GSK-3β*) phosphorylate β-catenin on serine/threonine residues, causing it to be sequestered to a "destruction complex" that includes adenomatous polyposis coli (*APC*) and axin, and its degradation through the 26S proteasome. Wnt signaling from the extracellular environment through the "canonical" frizzled receptor/low density lipoprotein receptor-related protein 5/6 (*LRP5/6*) pathway (*right*) results in phosphorylation of disheveled (*Dvl*), which directly or indirectly (through GSK-3β binding protein, *GBP*) phosphorylates and inactivates GSK-3β. GSK-3β inactivation allows β-catenin to avoid the destruction complex, accumulate within the cytoplasm, translocate to the nucleus, and trans-activate the transcription of genes associated with Dupuytren Disease development

Wnt signaling, ß-catenin accumulation, and the development of Dupuytren Disease. While it is unclear if Wnt expression is dysregulated in Dupuytren Disease-derived fibroblasts or myofibroblasts (O'Gorman et al. 2006), these SNP-associated changes may impact transcriptional responsiveness to biochemical or biomechanical stimuli, gene transcript stability, or enhanced interactions with other pathways that may "cross-talk" with the Wnt/ß-catenin pathway, such as TNFα signaling (Verjee et al. 2013).

In addition to the potential effects of SNPs in or near Wnt or Wnt-related genes, the Dupuytren Disease ECM can independently regulate ß-catenin levels in myofibroblasts. While ß-catenin levels are clearly increased in contracture tissues relative to the levels in syngeneic (genetically identical) fibroblasts in adjacent, macroscopically unaffected palmar fascia (Howard et al. 2003; Varallo et al. 2003), these levels are rapidly normalized and become indistinguishable from those in cells derived from macroscopically unaffected palmar fascia when cultured from explant tissues onto TCP (Varallo et al. 2003). Transferring these cells from TCP into three-dimensional collagen-based cultures under isometric tension in fibroblast-populated collagen lattice assays restores the increased levels of ß-catenin; however, a rapid

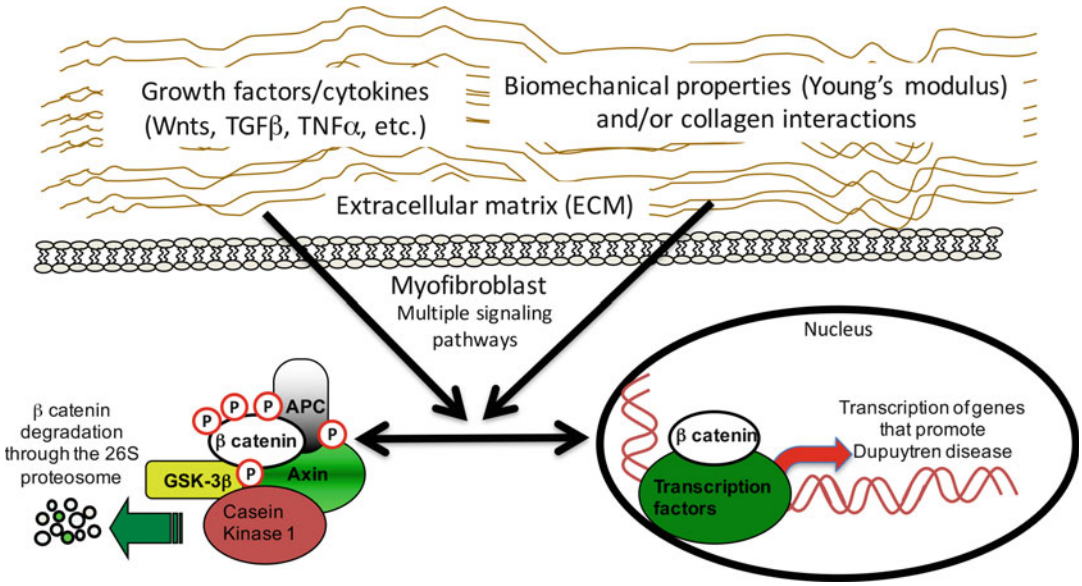

Fig. 6.3 The extracellular matrix regulates β-catenin levels. Many different cytokines, including transforming growth factor-β (*TGFβ*) and tumor necrosis factor α (*TNFα*), can signal through pathways that intersect with the Wnt/β-catenin signaling pathway and increase intracellular β-catenin levels. While the mechanisms are currently unclear, extracellular matrix (*ECM*) factors, such as collagen density, can increase or decrease intracellular β-catenin levels in Dupuytren Disease myofibroblasts, and thereby potentially modify β-catenin signaling in parallel with cytokine-activated pathways. As such, the potential confounding influences of the Dupuytren Disease ECM should be taken into account when assessing the effects of therapeutic interventions designed to modify cytokine or other signaling pathways that regulate β-catenin signaling in Dupuytren Disease

depletion of ß-catenin levels is evident once that tension is released (Varallo et al. 2003). In contrast, the dynamic regulation of ß-catenin levels in Dupuytren Disease myofibroblasts and ß-catenin levels in syngeneic myofibroblasts derived from macroscopically unaffected palmar fascia remain relatively stable under these conditions (Varallo et al. 2003). When cultured in low-density type-1 collagen substrates with little or no isometric tension, ß-catenin levels in myofibroblasts derived from contracture tissues are depleted over 72 h until they are virtually undetectable by immunoblotting (Vi, Njarlangattil, et al. 2009). While these culture conditions also induce some depletion of ß-catenin levels in syngeneic myofibroblasts derived from macroscopically unaffected palmar fascia, the effects are modest and variable between cultures (Vi et al. 2009b). TGFβ-1, the ECM-associated cytokine that is well known to promote the development of myofibroblasts (Badalamente et al. 1996), restores ß-catenin levels in Dupuytren Disease myofibroblasts cultured in low-density type-1 collagen substrates (Vi et al. 2009b). While it is currently unclear whether matrix stiffness, collagen signaling, or both are required to elicit these effects on ß-catenin levels in Dupuytren Disease myofibroblasts, it is clear that these cells are abnormally sensitive to these factors relative to syngeneic myofibroblasts derived from macroscopically unaffected palmar fascia.

These findings predict that the outcomes of Wnt/ß-catenin signaling analyses in Dupuytren Disease will be dependent on the culture substrates used during the analyses. Such effects are predicted to extend beyond the expression of genes that are trans-activated by ß-catenin and translated into fibrosis-associated proteins and may also include the cytokines and ECM-associated signaling molecules that act in parallel to enhance or attenuate Wnt/ß-catenin signaling. Thus, before we perform *in vitro* analyses of therapeutic interventions that modify Wnt/ß-catenin signaling in Dupuytren Disease, it is essential that we make informed choices regarding the

culture substrates in which such analyses take place (Fig. 6.3).

6.8 Targeting the Extracellular Matrix to Attenuate Dupuytren Disease Development

If we accept that the ECM surrounding Dupuytren Disease myofibroblasts modifies their responses and actively promotes disease progression, then the ECM itself can be considered as a therapeutic target. The concept of targeting the ECM in Dupuytren Disease is not new. J. T. Hueston, one of the "founding fathers" of Dupuytren Disease research, originally suggested that "enzymic fasciotomy" (Hueston 1971) could achieve similar outcomes to surgical fasciotomy in select patients. His approach was to use a cocktail of proteolytic enzymes and anti-inflammatory agents to degrade the ECM-associated collagens in contracture cords while simultaneously dampening the effects of pro-fibrotic inflammatory cytokines. While Hueston's approach did not gain broad acceptance at the time, targeting the ECM-associated collagens in contracture cords has now become a therapeutic reality. Xiaflex/Xiapex® (Hurst and Badalamente 1999; Badalamente et al. 2002; Hurst et al. 2009) is a mixture of *Clostridium histolyticum* type I and type II collagenases that specifically target the amino- and carboxy-termini and internal peptide residues of the type I and type III collagens in the Dupuytren Disease ECM. While this approach has many advantages over more invasive treatment options, it is worth noting that degradation of type I and type III collagens in the ECM, while effective for restoring hand function in the short term, is insufficient to prevent Dupuytren Disease recurrence (Watt et al. 2012; Baltzer and Binhammer 2013; Chen et al. 2011). The consequences of disrupting the biochemical and biomechanical signals that myofibroblasts receive from their collagen-enriched ECM under tension remain poorly understood at the molecular level and worthy of detailed investigation. Controlled proteolysis of collagens and other ECM proteins can generate bioactive molecules known as matricryptins (Ricard-Blum and Ballut 2011) that stimulate a wide variety of cellular responses including proliferation, migration, and angiogenesis (Ricard-Blum and Salza 2014). It is currently unclear whether matricryptins or other biologically active factors derived from ECM degradation contribute to Dupuytren Disease recurrence after Xiaflex/Xiapex® treatments.

While Xiaflex/Xiapex® has demonstrated the efficacy of targeting collagens in the Dupuytren Disease ECM, there is considerable potential to expand on this approach and target additional molecules in parallel to more effectively attenuate Dupuytren Disease recurrence. We could revisit the original approach by J. T. Hueston and combine Xiaflex/Xiapex® injections with TNFα inhibitors to dampen pro-fibrotic inflammatory responses. Alternatively, we could combine Xiaflex/Xiapex® injections with other novel interventions reported to prevent the reformation of a pro-fibrotic ECM by myofibroblasts, such as inhibitors of the nuclear factor κB (NFκB) pathway (Mia and Bank 2015) or lysyl oxidase (Barry-Hamilton et al. 2010). Hypothetically, we could also take advantage of the immune response to *Clostridium hystolyticum* type I and type II collagenases that more than 90% of patients develop after they receive Xiaflex/Xiapex® injections (Peimer et al. 2015). It may be possible to use Xiaflex/Xiapex® as a treatment and an adjuvant to promote a robust immune response to peptide antigens. These antigens could be modeled on cell surface or secreted molecules that are specifically expressed or upregulated in Dupuytren Disease myofibroblasts, such as Wilms' tumor 1 (Crawford et al. 2015). These hypothetical possibilities are only the "tip of the iceberg" of potential therapeutic interventions to target molecules that are in, or act in combination with, the Dupuytren Disease ECM. To expand our repertoire of interventions and achieve our goal of preventing Dupuytren Disease progression and recurrence, we need to gain a much more detailed understanding of the complexity of the Dupuytren Disease ECM and to explore its potential as a therapeutic target.

Conflict of Interest The author has no conflicts of interest to declare.

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Biomarkers of Postsurgical Outcome in Dupuytren Disease

7

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7.1 Introduction

Dupuytren Disease (DD) is a common disabling condition of the hand, affecting over 2 million people in the UK (Shaw et al. 2007; Townley et al. 2006). It is characterised by fibrosis of the palmar fascia. Initially there is a cellular hyperproliferation to produce nodules with deposition of collagen-rich cords. The combination of a cell-mediated contraction and remodelling of the extracellular matrix (ECM) leads to shortening of the tissue and deformity of the fingers (contracture). The only current treatment for Dupuytren contracture is surgery with high recurrence rates or minimally invasive treatments, like collagenase injection or needle fasciotomy, with even faster recurrence. Further surgery becomes more invasive with higher complication rates and incomplete contracture correction. There are no known drug treatments for the condition at present. The cellular and molecular mechanisms leading to Dupuytren contracture are poorly understood.

The matrix metalloproteinases (MMPs) are a family of 23 enzymes in man, including enzymes able specifically to degrade collagen (MMP-1, MMP-2, MMP-8, MMP-13 and MMP-14) (Kessenbrock et al. 2010). A related family of 19 metalloproteinases, the ADAMTSs, include the major aggrecan-degrading proteinases and three procollagen N-propeptidases which are

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important in the synthesis of collagen (ADAMTS-2, ADAMTS-3 and ADAMTS-14) (Kelwick et al. 2015). There are four specific inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), with varying selectivity against the proteases (Brew and Nagase 2010). Normal ECM turnover requires a balance between metalloproteinase and inhibitor activities with fibrosis coming from an imbalance away from proteolysis (Kessenbrock et al. 2010). The MMPs are implicated in tumour invasion and metastasis. When MMP inhibitors underwent clinical trials in cancers (Vandenbroucke and Libert 2014), the major side effect was a 'musculoskeletal syndrome', described as frozen shoulder and/or a condition resembling DD (Hutchinson et al. 1998). The inhibitors were 'pan-MMP' inhibitors, showing ~ nanomolar Ki against many of the MMPs tested. The musculoskeletal syndrome is ascribed to the inhibition of non-target metalloproteinases both within and outside of the MMPs.

Whilst subsets of MMPs and TIMPs had been measured in DD tissue, we assayed the expression of the entire *MMP*, *TIMP* and *ADAMTS* gene families in DD tissue (nodule and cord) compared to normal palmar fascia using qRT-PCR. The expression of four key collagen-degrading proteinases, *MMP1*, *MMP2*, *MMP13* and *MMP14* as well as *TIMP1*, was significantly raised in DD nodule, as was the expression of a collagen biosynthetic enzyme *ADAMTS14*. We concluded that palmar fibrosis and finger contracture in DD may result from (i) increased collagen biosynthesis with processing mediated by increased ADAMTS-14, (ii) elevated TIMP-1 blocking MMP-1- and MMP-13-mediated collagenolysis (with these enzymes elevated in an attempt to resolve the fibrosis), and (iii) contraction enabled by MMP-14 (and MMP-2-)-mediated pericellular collagenolysis which escapes inhibition by TIMP-1 (Johnston et al. 2007). We also followed DD patients for 2 years and assessed their hand function and disease recurrence after surgery. We discovered that the expression of key MMPs (e.g. *MMP1*, *MMP2*, *MMP13* and *MMP14*) and *TIMP1* correlates with poor progression post-fasciectomy (Johnston et al. 2008). This reinforces their role as key mediators of the disease process.

Recently we have used *in vitro* models of cell-mediated contraction to investigate the function of key proteinases and inhibitors that we have identified in DD tissue (Wilkinson et al. 2012). In fixed fibroblast-populated collagen lattice (FPCL) models, broad spectrum synthetic MMP inhibitors block contraction (Daniels et al. 2003; Townley et al. 2008). This blockade is difficult to dovetail with the reported side effects of pan-MMP inhibitors in clinical trials, where Dupuytren-like contracture was observed (Hutchinson et al. 1998). However, this reflects our increasing understanding that MMPs can mediate positive, as well as negative, effects (Kessenbrock et al. 2010), and the need is to identify specific MMPs as therapeutic targets (Vandenbroucke and Libert 2014). Dupuytren fibroblasts do show increased contraction in the FPCL model, which is a relevant feature of DD (Bisson et al. 2004). It was therefore important both to understand the role of specific metalloproteinases in the model. We profiled expression of all *MMPs*, *ADAMTSs* and *TIMPs* in DD cells within FPCL both during the development of tension and following release (Wilkinson et al. 2012). *MMP1*, *MMP2*, *MMP3*, *MMP13*, *MMP14* and *TIMP1* all show increased expression in the 3D collagen lattice compared to monolayer culture. *MMP1*, *MMP3*, *MMP14* and *TIMP1* all then show decreased expression under tension, with increase upon release, whilst *MMP13* shows a steady increase across the assay that may simply reflect response to the collagen lattice, and *MMP2* is not regulated at this level. To examine the role of each of MMP-1, MMP-2, MMP-3, MMP-13 and MMP-14, an siRNA approach was developed to knock each gene down individually. Knockdown of *MMP2* and particularly *MMP14* led to decreased contraction of the collagen lattice with slower kinetics, demonstrating a key role for these proteinases. Knockdown of *MMP1* gave a more rapid contraction in the early phase of the assay, leading us to speculate that the action of MMP-1 may be

to decrease tension in the fixed phase of the lattice. Knockdown of *MMP3* or *MMP13* had no significant effect on contraction, and therefore these proteases do not have an essential role in contraction.

Leading on from the correlation between gene expression and tissue levels of specific MMPs and their role in contraction, we hypothesised that circulating levels of collagen-degrading MMPs, MMP-1, MMP-13 and MMP-14 may be biomarkers of disease progression and/or postsurgical recurrence. If proven, this could lead to a blood test which would guide surgical decision making. MMPs (MMP-1, MMP-2, MMP-9) and TIMPs (TIMP-1 and TIMP-2) have been measured in the sera of patients with DD compared to patients undergoing carpal tunnel release, with significantly higher TIMP-1 levels measured in DD patients (Ulrich et al. 2003). However, these data were not compared to measurements of DD.

7.2 Materials and Methods

7.2.1 Patient Samples

All surgery was performed at the Norfolk and Norwich University Hospital under approval from the local research ethics committee; all patients gave informed consent. Dupuytren Disease tissue was taken at fasciectomy ($n=25$, age range 50–78 years, 5 female, 20 male). Samples were divided into regions of nodule and cord according to gross morphology. Normal palmar fascia was taken from patients without DD undergoing carpal tunnel release ($n=30$, age range 31–88 years, 20 female, 10 male). Tissue was dissected into approximately 5 mm pieces and snap frozen in liquid nitrogen within 15–30 min of surgery. Blood was taken from patients immediately prior to surgery into sodium citrate. Within 60 min, it was centrifuged at 1600 g for 15 min at 4 °C and plasma removed and stored in aliquots at −80 °C. Total extension deficit was measured with a goniometer, with deficit from affected digits added together.

7.2.2 RNA Isolation and qRT-PCR

TRIzol reagent (Life Technologies) was used to isolate total RNA from tissue, with the aqueous fraction from the phase separation further purified using the RNeasy Mini Kit (Qiagen). Reverse transcription used 1 μg total RNA (DNase treated) and SuperScript III with random hexamers. Data from qRT-PCR was normalised to expression of 18S ribosomal RNA. Fluorescence for each cycle was analysed by the real-time PCR 7500 system (Applied Biosystems).

7.2.3 Microarray Analyses

Profiling of mRNA used the Illumina Human HT12v4 platform (Source Bioscience). Data were analysed using the Bioconductor packages (http://www.bioconductor.org) in R (http://www.r-project.org). Data were firstly preprocessed by background correction, variance stabilisation and normalisation using the quantile method.

7.2.4 Enzyme-Linked Immunosorbent Assays (ELISA)

Commercial kits were used to measure MMPs by ELISA according to manufacturer's instructions. MMP-1, R&D Systems DuoSet, human total MMP-1 #DY991; MMP-13, R&D Systems DuoSet, human total MMP-13 #DY511; MMP-14, Cloud Clone US #SEC056Hu. Samples were diluted 1:2 for measurement of both MMP-1 and MMP-14 and 1:4 for measurement of MMP-13.

7.2.5 Statistics

Correlation analyses used either Pearson correlation for normally distributed data or Spearman's rank correlation for non-parametric data. For array data, the rank of their expression level across all samples was computed and compared to the rank of clinical measurements to give the Spearman's rank correlation.

7.3 Results

7.3.1 Measurement of Total Extension Deficit (TED)

In patients undergoing fasciectomy ($n=25$), a number of measurements of hand function were taken preoperatively and then at an intermediate time (up to 12 weeks) after surgery and postoperatively after approximately 1 year. Total extension deficit (TED) is a measure of contracture of the digits. Figure 7.1 shows that 24 patients had the expected decrease in TED after surgery. Between the intermediate and postoperative measurements, 9 patients have continued decrease in TED, 4 patients have no change (all have zero TED) and 5 have increased TED, with 7 having incomplete data.

7.3.2 Correlation of Gene Expression with TED

Initially, the expression of *MMP1*, *MMP13* and *MMP14* was measured at the mRNA level in Dupuytren Disease tissue taken at fasciectomy. Gene expression was correlated with TED taken preoperatively, immediately postoperatively (intermediate) and then at one year postoperatively (as in Sect. 7.3.1). Compared to our previous study (Johnston et al. 2008), there was little correlation in this cohort, with a statistically significant correlation between MMP1 expression and the change between preoperative and one year postoperative TED (Fig. 7.2a). A correlation was also measured between MMP14 expression and the change between intermediate and one year postoperative TED, approaching statistical significance (Fig. 7.2b).

7.3.3 Correlation of Circulating MMPs with TED

The level of MMP-1, MMP-13 and MMP-14 was measured in plasma taken preoperatively and correlated with measurements of TED. Whilst there was no correlation with postoperative progression of TED (i.e. disease recurrence), a correlation was seen between the circulating level of MMP-14 and preoperative TED (Fig. 7.3) which approached statistical significance.

7.3.4 Correlation of Gene Expression with TED

RNA from ten Dupuytren nodules was subjected to whole genome array to measure total gene expression. These were then subjected to correlation

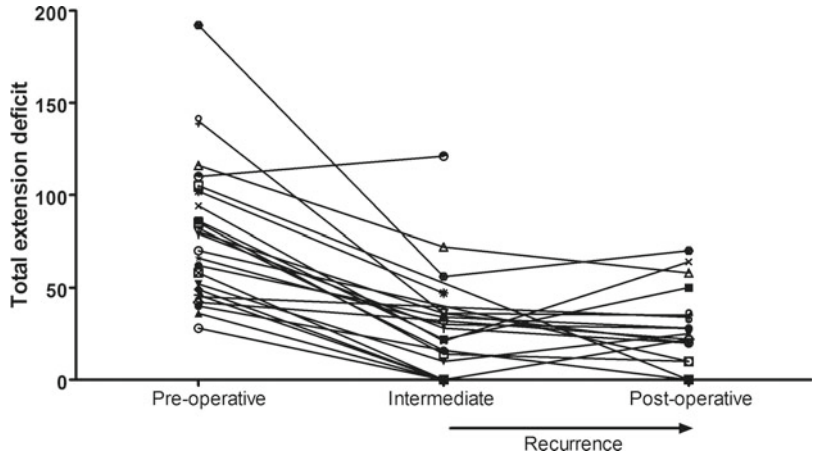

Fig. 7.1 Measurement of total extension deficit. Patients ($n=25$) underwent fasciectomy for Dupuytren Disease. Total extension deficit was measured with a goniometer, with deficit from affected digits added together. Measurement was taken preoperatively, at an intermediate stage (up to 12 weeks after surgery), and then postoperatively at approximately 1 year

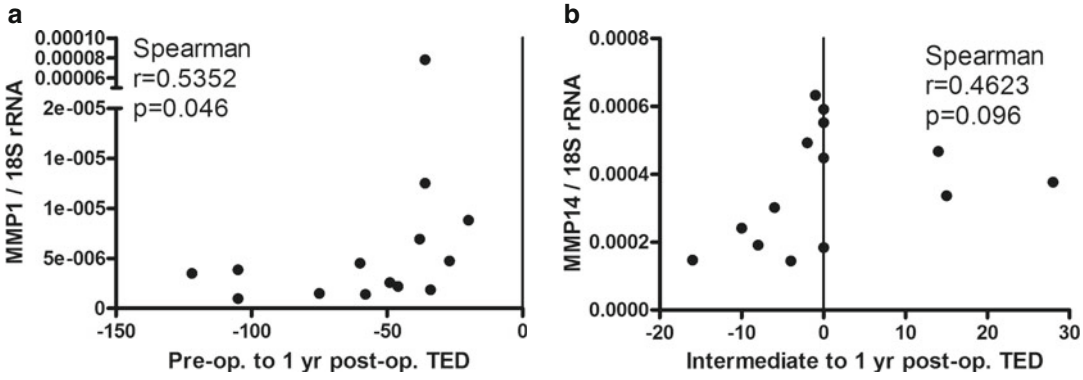

Fig. 7.2 Correlation between gene expression in nodule tissue and total extension deficit. Expression of matrix metalloproteinase (*MMP*) gene expression ((**a**) *MMP1* and (**b**) *MMP14*) was measured by qRT-PCR in tissue (nodule) taken at fasciectomy ($n = 14$) and correlated with change in total extension deficit

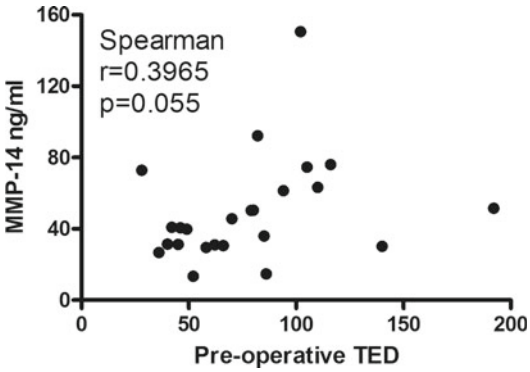

Fig. 7.3 Correlation between measurement of circulating MMP-14 and total extension deficit. Matrix metalloproteinase-14 (*MMP-14*) was measured in the plasma of patients with Dupuytren Disease ($n = 25$) in advance of fasciectomy and correlated with total extension deficit

analyses. Interestingly, the expression of a number of genes was correlated with either preoperative TED (e.g. ASPN, asporin, Fig. 7.4a) or postoperative TED (e.g. fucosyltransferase 1, FUT1, Fig. 7.4b).

7.4 Discussion

There are a number of genes/proteins associated with DD, coming from genetic studies, e.g. Dolmans et al. (2011); microarray analyses, e.g. Shih et al. (2012b); or targeted approaches, e.g. Raykha et al. (2013). Any of these proteins which are extracellular have the potential to be biomarkers of disease.

We sought to explore the utility of collagen-degrading proteases (MMP-1, MMP-13 and MMP-14) as circulating biomarkers of postsurgical recurrence of Dupuytren Disease after fasciectomy. Twenty-five patients undergoing fasciectomy were recruited, taking a blood sample preoperatively. Tissue was then collected at surgery for gene expression analyses.

Measurement of TED showed the expected decrease immediately postoperatively, with patients then progressing either to a further decrease in TED or an increase. This increase in TED between the immediately postoperative stage and then at one year was deemed to be recurrence of disease.

Whilst our earlier studies had shown correlation between the tissue expression of *MMP1*, *MMP13* and *MMP14* and disease recurrence defined in this way, there was only poor correlation in the current study. This may simply reflect variation in patient cohorts.

Similarly there was no correlation between disease recurrence and the circulating level of any of the MMPs. However, there was a correlation between circulating MMP-14 and preoperative TED which adds to evidence from ourselves (Johnston et al. 2007, 2008; Wilkinson et al. 2012) and others (e.g. Shih et al. 2012a) that MMP-14 has a role in the mechanisms underlying Dupuytren Disease.

There are many reasons why gene expression and protein levels might not correlate and there are a number of issues in measurement of the

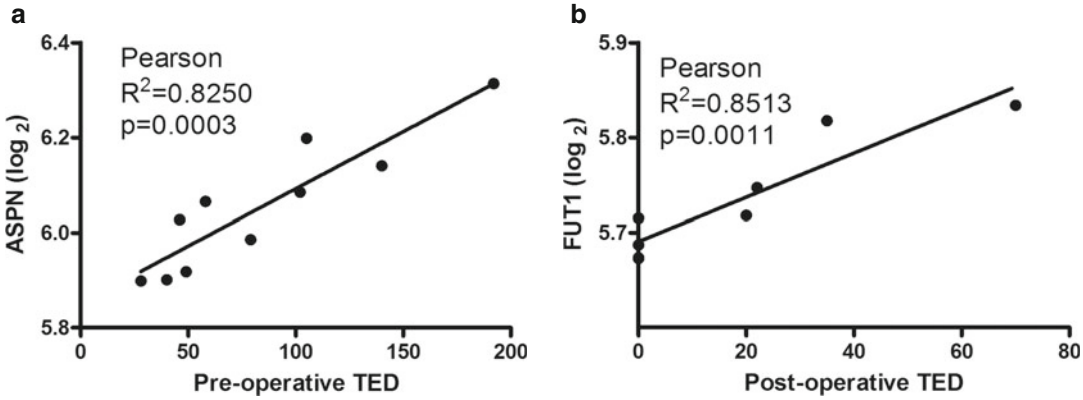

Fig. 7.4 Correlation between gene expression by microarray and total extension deficit. Gene expression was measured in a subset of Dupuytren patients ($n = 10$) by microarray. Gene expression was correlated with total extension deficit. (**a**) ASPN, asporin; (**b**) FUT1, fucosyltransferase 1

proteins. MMPs are synthesised as proenzymes, which are activated concomitant with the removal of their propeptide; the active enzymes can then be inhibited by TIMPs, giving an enzyme/inhibitor complex (Vandenbroucke and Libert 2014). ELISA assays, which rely on the recognition of specific epitopes by antibodies, are unlikely to measure all of these forms, and so there may not be a direct correlation between mRNA and protein measured by ELISA. Also, MMP-14 is a membrane-bound protease, so its level in the circulation is dictated by its shedding from the cell membrane (Itoh 2015). These all have the potential to confound the data. Furthermore, measurement of protein does not provide information about activity itself for these proteinases.

An unbiased approach, measuring the entire transcriptome, uncovered many genes whose expression correlates with either preoperative or postoperative TED (of which two are shown in Fig. 7.4). The measurement of these genes needs to be confirmed using qRT-PCR in order to demonstrate that they are not false-positives derived from multiple testing.

Conclusions

There is a strong need to identify biomarkers with which either to stratify Dupuytren Disease or to predict disease progression or recurrence. Whilst our data suggest that the collagen-degrading MMPs do not fit these criteria, the correlation of circulating MMP-14 with preoperative TED suggests its involvement in the disease process. Genes (and the proteins they encode) identified through high-throughput transcriptomics will be further pursued.

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8 Tumour Necrosis Factor as a Therapeutic Target in Dupuytren Disease

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Contents

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8.1 Dupuytren Disease: Prevalence and Limitation of Current Treatments for Late Disease

Dupuytren Disease is a very common disorder, affecting 4 % of the general population in the US and UK and is more prevalent in northern Europe (Hindocha et al. 2009; Lanting et al. 2013). Patients typically present for treatment when they have developed fixed flexion deformities of the digits leading to impairment of hand function (Legge and McFarlane 1980).

Treatment is therefore directed to correct the deformities and usually involves surgical excision of the diseased tissue (fasciectomy or dermofasciectomy), division of the cord with a needle (needle aponeurotomy) or collagenase injection into the cord. Each of these techniques has limitations. Whilst recurrence rates for surgery are typically low, of the order of 10 % at 3 years for fasciectomy (Ullah et al. 2009) and even lower for dermofasciectomy (Armstrong et al. 2000), postoperative recovery can be prolonged and patients often require extensive hand

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therapy (Hughes et al. 2003; Larson and Jerosch-Herold 2008). The less invasive procedures may be preferred by patients due to more rapid post-treatment recovery, but recurrence rates are typically higher, reported as 70 % for needle aponeurotomy (van Rijssen et al. 2012) and 35 % for clostridial collagenase (Peimer et al. 2013) at 3 years. Therefore, although usually described as a fibroproliferative disorder, current treatments are reserved for patients with later stage disease, focussed on treating the fibrous cord. An economic analysis of these treatments reported that neither surgical fasciectomy nor collagenase represented cost-effective use of healthcare resources (Chen et al. 2011). Hence, there is an urgent unmet need to develop an effective treatment for patients at an early stage and to prevent disease progression and recurrence.

8.2 Stages of Dupuytren Disease and Progression

One of the earliest classifications of Dupuytren Disease was into three stages according to the histological appearance, namely, proliferative, involutional and residual (Luck 1959). This was further refined by correlating with the clinical findings and ultrastructural features (Rombouts et al. 1989):

I. *Early*. Clinically the disease is characterised by the presence of nodules on the palmar aspect of the hand but lack of flexion deformities of the digits. Histologically, mitotic figures are seen, indicating the cells are actively proliferating.
II. *Active.* This stage is characterised by increasing flexion deformity of the digit(s) but not necessarily with the presence of clinically detectable nodules. Histologically the tissue has a fibrocellular appearance characterised by high cellularity but absence of mitoses.
III. *Advanced disease.* Clinically the condition is long-standing and has not deteriorated over recent months. At the histological level the cord appears fibrous, mainly composed of collagen, with relatively few cells.

There was an attempt to refine the staging according to the composition of the collagenous cord based on the observation that earlier lesions have a higher proportion of type III collagen, and this changes to a greater proportion of type I collagen at the later stages of the disease (Lam et al. 2010):

I. 35 % type III collagen
II. >20 % type III collagen
III. <20 % type III collagen

One of the few groups to study tissues collected at all clinical stages of the disease also classified the disorder into 3 stages (Chiu and McFarlane 1978):

I. *Early disease.* These specimens comprised nodules from patients with no digital contracture. The tissue comprised proliferating spindle-shaped cells that were surrounded by fine granulofibrillary material, but there was no increased collagen deposition in the nodule.
II. *Active disease.* Clinically these patients presented with palmar thickening with associated joint contracture, which on average occurred over 3 years. The nodules comprised mainly of myofibroblasts with very little intervening collagen. The myofibroblasts were characterised by bundles of microfilaments and prominent intercellular junctions. The nodules were associated with cords, which were relatively acellular
III. *Advanced disease*. These patients had progressive joint contracture for more than 3 years. Microscopic examination revealed relatively few cells that were elongated and embedded in stroma comprising a large amount of mature collagen fibres.

Studies on surgically excised specimens from patients with digits flexed to 30° or greater and with functional impairment of the hand show that even in this group of patients nodules comprising aggregates mainly of myofibroblasts with interspersed inflammatory cells are embedded within the cords and anatomically lie adjacent to the

flexed joint (Verjee et al. 2009). Furthermore, patients with more advanced deformities are less likely to have identifiable nodules (Verjee et al. 2009), corresponding to the advanced stage described by Chiu et al. (Chiu and McFarlane 1978).

However, it is not clear that all patients with early nodules will progress to develop flexion deformities of the digits. An 18-year follow-up study of an Icelandic male population found that 35% of patients with early nodules developed flexion contractures. In a US population, approximately 50% of patients with early disease progressed to cords, including 8.5 % with flexion deformities, over an 8.5 year period (Reilly et al. 2005).

8.3 Myofibroblasts and Models

8.3.1 Myofibroblasts

The cell responsible for both the matrix deposition and contraction in all fibrotic disorders is the myofibroblast (Wynn and Ramalingam 2012). First described in granulation tissue (Gabbiani et al. 1971; Majno et al. 1971), the cells are characterised by the expression of α-smooth muscle actin (α-SMA) (Skalli et al. 1986), the contractile protein present in smooth muscle cells. In myofibroblasts the α-SMA is present in stress fibres that respond to tension and enable the cell to contract the surrounding matrix. Mechanical stress is an important driver of myofibroblast activation and fibrosis (Hinz 2010, 2015a, b; Ho et al. 2014). The myofibroblasts form specialised junctions called fibronexi with the surrounding matrix (Fig. 8.1a) (Yannas 1998; Singer et al. 1984; Hinz and Gabbiani 2003) and effectively function together as a syncytium through specialised intercellular junctions (Fig. 8.1b) (Verhoekx et al. 2013).

8.3.2 Model Systems

There is no animal model for Dupuytren Disease. In vivo models rely on allotransplantation of excised human tissue into immunodeficient rodents (Kuhn et al. 2001; Satish et al. 2015). Specimens have also been maintained *ex vivo* in tissue culture for periods up to 7 days (Karkampouna et al. 2014). An alternative approach is to study isolated cells in culture. However, there are significant limitations to studying fibroblasts in 2D cultures on plastic compared to 3D matrices (Cukierman et al. 2001). Consequently, many groups have investigated the behaviour of these cells in collagen matrices (Grinnell 1994, 2000; Grinnell and Petroll 2010; Tomasek et al. 1992, 2002). We found that even in 3D matrices Dupuytren myofibroblasts lose their

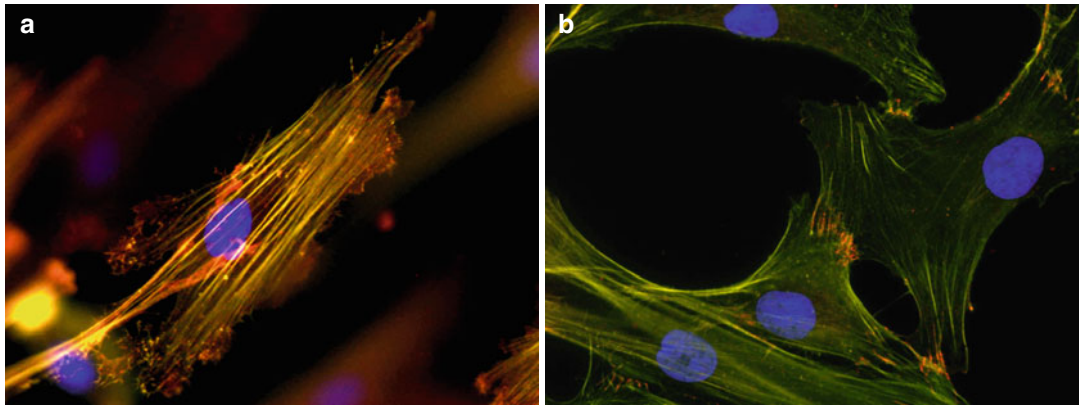

Fig. 8.1 Dupuytren myofibroblasts. (**a**) Immunofluorescence staining of Dupuytren myofibroblasts in a 3D collagen matrix. Cell matrix junctions stained for integrin β1 (*red*), F actin (phalloidin) (*green*) and nuclei stained with DAPI (*blue*). (**b**) Immunofluorescence staining of Dupuytren myofibroblasts in monolayer. Intercellular junctions stained for β catenin (*red*), F actin (phalloidin) (*green*) and nuclei stained with DAPI (*blue*)

contractility unless they remain under stress (Verjee et al. 2010). A system for measuring cell contractility in 3D collagen matrices (Eastwood et al. 1994) was used to compare Dupuytren myofibroblasts with control fibroblasts derived from carpal ligament (Bisson et al. 2004) or the dermis of palmar or non-palmar skin from patients with Dupuytren Disease (Verjee et al. 2010). The authors found that under isometric conditions fibroblasts reached tensional homeostasis, whilst myofibroblasts continued to contract.

8.3.2.1 Control Cells

When studying the pathogenesis of Dupuytren Disease, it is important to use appropriate controls. Many previous studies have compared cells from Dupuytren nodules or cords with cells from the fascia in the region of the carpal tunnel or the transverse carpal ligament from affected or normal individuals or uninvolved transverse palmar fibres from patients with Dupuytren Disease. However, this approach has limitations. The palmar fascia over the carpal tunnel is rarely affected by Dupuytren Disease in susceptible individuals, and the transverse carpal ligament is never involved; hence, it is possible that the constituent cells are inherently different (Satish et al. 2012). Furthermore, with the exception of nodules in Dupuytren Disease, fascia is sparsely populated by cells, and hence to obtain adequate numbers, most authors use cells to passage 5 (Bisson et al. 2003). However, we and others have shown that at passage 5 the phenotypes of myofibroblasts and normal human dermal fibroblasts tend to merge (Rehman et al. 2012; Verjee et al. 2010). In addition, whereas the cell of origin for Dupuytren myofibroblasts remains controversial, there is accumulating evidence that the adjacent tissues, including the peri-nodular fat and overlying dermis, make a significant contribution (Iqbal et al. 2012). Moreover, Dupuytren Disease is restricted to the palm of the hands in patients with a genetic predisposition. Therefore, it is important to avoid variations due to genetic and environmental factors. For these reasons, we compared dermal fibroblasts from palmar and non-palmar sites from the same group of patients, using palmar dermal fibroblasts from individuals without Dupuytren Disease as controls (Verjee et al. 2013). The restriction of Dupuytren Disease to the palm of genetically susceptible individuals suggests that there may be epigenetic regulation of precursor cells. Hence, it would be appropriate to compare cells from affected and unaffected regions of the same individual.

8.4 Cells and Cytokines in Dupuytren Disease

8.4.1 Characterisation of Cell Types

Several studies have sought to characterise the cells in Dupuytren Disease. We found that the majority of the myofibroblasts are concentrated in histological nodules in excised cords (Verjee et al. 2009), and within these nodules, approximately 90% of the cells are α-SMA positive (Verjee et al. 2013). Several authors have demonstrated the presence of immune cells in nodules, including macrophages and T cells (Andrew et al. 1991; Baird et al. 1993; Meek et al. 1999; Sugden et al. 1993; Verjee et al. 2013). The group that did not find any CD68+ macrophages cells on immunostaining did not show their positive controls (Bianchi et al. 2015). In our view the data from several groups using immunostaining and FACS analysis of freshly disaggregated cells from Dupuytren Disease confirms the presence of immune cells in Dupuytren nodules, where the macrophages appear to localise predominantly in the vicinity of the blood vessels (Verjee et al. 2013).

8.4.2 Cytokines and Growth Factors in Dupuytren Disease

A number of studies examining the expression of cytokines and growth factors by RT-PCR or immunohistochemistry identified IL1-α, IL-1β, TGF-β, FGF and VEGF in Dupuytren tissue (Baird et al. 1993; Berndt et al. 1995; Badalamente et al. 1996; Bianchi et al. 2015; Ratajczak-Wielgomas et al. 2012). We studied the cytokines in the supernatant secreted by freshly disaggregated cells from Dupuytren nodules, analogous

to the experiments that led to the identification of TNF as a therapeutic target in rheumatoid arthritis (Brennan et al. 1989). Over a 24-h period, during which the inflammatory cells remained viable in culture without the addition of exogenous growth factors, we detected TGF-β1, TNF, IL-6 and GM-CSF; levels of IL-1β, IL-10 and IF-γ were very low (Verjee et al. 2013). We have subsequently found that the levels of secreted TNF remained unchanged over a range of cell concentrations (1.5×10^5–1×10^6 cells in 2 ml culture media). By passage 2 the inflammatory cells had been lost, and levels of TNF in cell culture supernatants fell to near zero, whilst levels of TGF-β1 increased over 2 fold, the latter through autocrine secretion by myofibroblasts in culture (Verjee et al. 2013). These findings highlight the importance of studying primary cells to identify potential therapeutic targets and may go some way towards explaining the lack of efficacy of all late phase clinical trials to date targeting TGF-β1 for fibrotic diseases (Hawinkels and Ten Dijke 2011; Varga and Pasche 2009). The published data suggest that Dupuytren Disease is a localised inflammatory disorder, and it has been suggested that all fibrosis occurs as result of preceding inflammation (Wick et al. 2013).

8.4.3 Role of Secreted Cytokines

We compared the effects of the secreted cytokines on early passage palmar dermal fibroblasts from patients with Dupuytren Disease with control fibroblasts from the palmar skin of normal individuals and the non-palmar dermis of patients with Dupuytren Disease (Verjee et al. 2013). Predictably, TGF-β1 led to the differentiation of all three types of dermal fibroblasts into myofibroblasts but only at relatively high (1–10 ng/ml) concentrations. For comparison, freshly disaggregated cells from Dupuytren nodules in culture secreted 236 ± 248 pg/ml TGF-β1. TNF at concentrations of 50–100 pg/ml led to the differentiation of only palmar dermal fibroblasts from Dupuytren patients into myofibroblasts. At these levels, TNF had no effect on the control dermal fibroblasts, whilst higher concentrations (1–10 ng/ml) resulted in downregulation of their contractile activity, as previously reported (Goldberg et al. 2007). For comparison, freshly disaggregated nodular cells secreted 78 ± 26 pg/ml of TNF (Verjee et al. 2013).

8.4.4 TNF Signalling Pathways in Dupuytren Disease

The different responses to TNF of the various cell types may in part be related to enhanced expression of TNF receptors at both mRNA and protein level, in particular TNFR2 by palmar dermal fibroblasts from Dupuytren patients and by the Dupuytren myofibroblasts (Verjee et al. 2013).

A number of genetic studies have identified an association between the Wnt signalling pathway and Dupuytren Disease (Anderson et al. 2014; Dolmans et al. 2011). However, the expression of Wnts was found not to account for the dysregulated expression of β-catenin in Dupuytren Disease (O'Gorman et al. 2006). We found that only in palmar dermal fibroblast from Dupuytren patients, but not in control cells, there was crosstalk between TNF and canonical Wnt signalling pathways, whereby treatment of the cells with TNF led to inhibition of GSK-3β, which in turn leads to preservation of β-catenin from degradation (Fig. 8.2) (Verjee et al. 2013). The β-catenin translocates to the nucleus and upregulates the transcription of profibrotic genes, including for α-SMA and COL-1A1. The β-catenin is also a key component of intercellular adherens junctions. The crosstalk between TNF and Wnt signalling pathways has previously been shown in pre-adipocytes (Cawthorn et al. 2007; Hammarstedt et al. 2007).

8.5 Translation of Laboratory Findings to the Clinic

Based on our clinical findings, we are proceeding with early phase trial for patients with Dupuytren Disease (RIDD – *r*epurposing ant*i*-TNF for *D*upuytren's *d*isease; (http://www.hra.nhs.uk/news/research-summaries/repurposing-anti-tnf-for-treating-dupuytrens-disease/). The

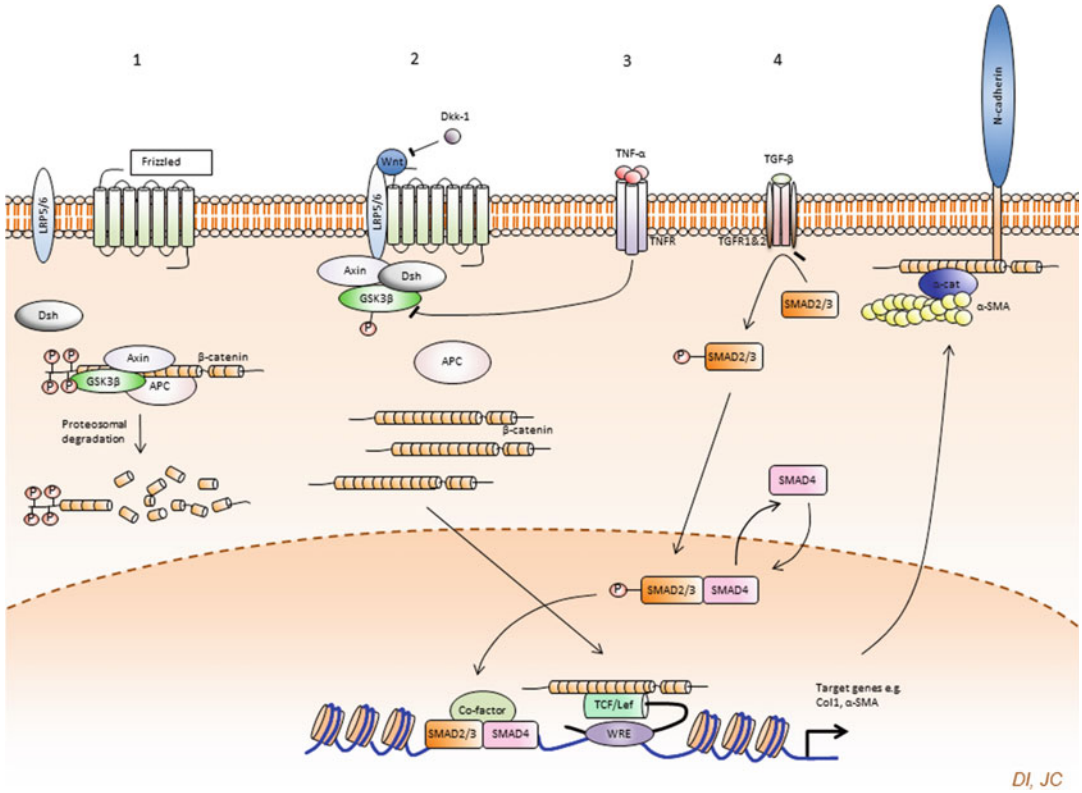

Fig. 8.2 Schematic illustrating how TNF acts via the canonical Wnt pathway, leading to the development of the myofibroblast phenotype. (*1*) In the resting state, cytoplasmic β-catenin is phosphorylated by GSK-3β. This modification targets β-catenin for ubiquitination and proteasomal degradation. (*2*) Ligation by Wnt of the receptor complex comprising Frizzled and LRP5/6 leads to phosphorylation and inhibition of GSK-3β. Thus, β-catenin escapes modification and subsequent degradation, leading to accumulation of cytoplasmic β-catenin, which participates in intercellular cell adherens junctions and also translocates to the nucleus. Here it binds to the transcription factors TCF/Lef and promotes the expression of genes typically associated with myofibroblasts: COL1 and α-SMA. Subsequent cytoskeletal assembly of α-SMA protein produces the contractile apparatus of the cell, with attachments to neighbouring cells via cadherins and the matrix via integrins. Wnt ligand– receptor binding is competitively inhibited by Dkk-1, leading to resumption of β-catenin degradation. (*3*) In palmar dermal fibroblasts from patients with Dupuytren Disease, TNF binding to TNFR leads to GSK-3β phosphorylation and inhibition, thereby releasing β-catenin from degradation and enabling the transcription of COL1 and α-SMA genes and assembly of an α-SMA-rich cytoskeleton. (*4*) Binding of TGF-β1 to TGF-β1R1/2 leads to Smad2/3 phosphorylation and activation. The latter recruits Smad4 and, on entering the nucleus, leads to transcription of the same genes as the β-catenin TCF/Lef complex, namely, COL1 and α-SMA (Adapted from Verjee et al. (2013))

trial is funded by the Health Innovation Challenge Fund (Wellcome Trust + Department of Health) and the study drug funded by 180 Therapeutics. The initial study will involve 40 patients with established Dupuytren Disease who are scheduled to undergo fasciectomy. Nodules identified preoperatively will be injected with varying doses of adalimumab or placebo, and the surgically excised specimens will be analysed in the lab for myofibroblast activity. In parallel, we are proceeding with a randomised double-blind trial of either adalimumab or placebo into the nodule of patients with early disease who show signs of progression. Patients will receive injections every 3 months for one year and then be followed for another 6 months. Outcome measures will include nodule hardness, size of the nodule on ultrasound scan, patient-reported outcome measures and assessment of hand function.

Conclusion

1. Early stages of Dupuytren Disease are characterised by the presence of highly cellular nodules.
2. The majority of the cells in the nodules are myofibroblasts.
3. Nodules also contain immune cells, including macrophages and T cells.
4. The nodular cells secrete cytokines, including TGF-β1 and TNF.
5. Only TNF selectively converts precursor dermal fibroblasts from the palm of patients with Dupuytren Disease into myofibroblasts.
6. There is crosstalk between TNF and Wnt signalling pathways in these cells.
7. TNF inhibition has proven safe and efficacious in inflammatory arthritis and inflammatory bowel disease.
8. We are proceeding with a clinical trial to assess the efficacy of TNF inhibition by adalimumab in patients with early Dupuytren Disease by local injection of the drug into the nodule.

Conflict of Interest JN has received research support and consultation fees and is a shareholder in 180 Therapeutics. IZ has no conflicts of interest.

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Contraction Versus Contracture: Considerations on the Pathogenesis of Dupuytren Disease

9

Hanno Millesi

Contents

9.1 Introduction

Dupuytren contracture (DC) is regarded as a strange disease occurring on the palmar side of the hand. Following cell proliferation, collagen tissue is produced, forming thick bands. These bands shrink and cause deformities and loss of certain hand functions. DC usually does not cause pain and is not life threatening.

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In spite of intensive research spanning more than 150 years, we still do not know:

1. How Dupuytren Disease starts.
2. To what extent similar diseases at the plantar aponeurosis (Ledderhose Disease) and at the tunica albuginea (Peyronie disease) are related to Dupuytren Disease and why.
3. Why other adjacent collagen structures such as the flexor tendons are never involved.
4. The mechanism of shrinkage. Is it a process of active contraction similar to the shortening of muscle, or is it a passive contracture similar to a post-immobilization joint contracture?

9.2 The Involved Tissue of the Hand

A fundamental understanding of Dupuytren Disease and its pathogenesis will require taking into account the specific tissue and function of the hand. All tissue at the palmar side of the hand which is necessary to perform a soft and a firm gripping function may be involved in DC. Millesi (1959) performed anatomical studies of this tissue describing it as *dense connective tissue body of the palmar side of the hand* (Figs. 9.1 and 9.2). Flint (1990) used the term *palmar connective tissue continuum*.

One common feature of the connective tissues composing the dense connective tissue body of the palmar side of the hand is that they contain a high

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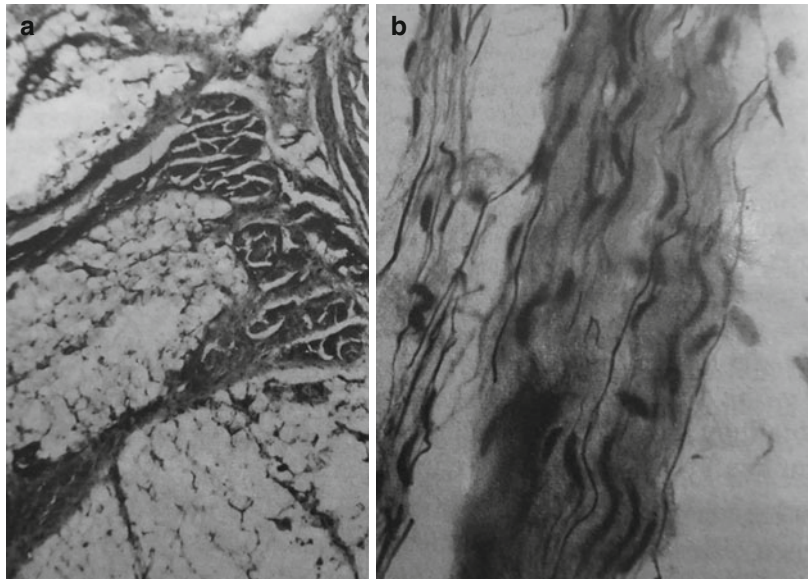


Fig. 9.1 Normal palmar aponeurosis. (**a**) Transverse section palmar aponeurosis. The skin is on the left side. Collagen fiber bundles ascend to the skin between fat lobules forming a three-dimensional network to permit soft gripping and distribute pressure. These fiber bundles emerge from the palmar aponeurosis, which fills the right upper quarter of the picture. The fiber bundles are cut transversely. In the right upper angle, one sees longitudinally cut collagen fibers, which belong to the deep transverse ligament of the palm. Hematoxylin–eosin, 1:28. (**b**) *Center*: Two collagen fiber bundles with collagen fibers showing the crimp structure of the collagen fibers and very few tiny elastic fibers between. This corresponds to a tension-bearing fiber bundle of a tendon. *Left side*: A fiber bundle with few collagen fibers and relatively more elastic fibers. This corresponds to gliding tissue. Prantner's elastic stain, 1:250

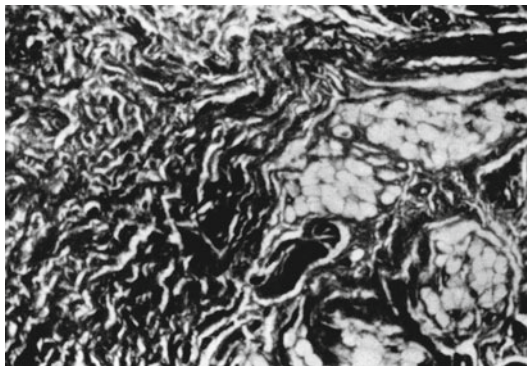


Fig. 9.2 Dermis–aponeurosis connections. An ascending collagen fiber bundle from the palmar aponeurosis merges into the dermis. This figure demonstrates the formation of a functional unit between the dermis, the ascending collagen fibers, the palmar aponeurosis, and the whole tension transmitting system of the palmar side of the hand. It is impossible to define a border between collagen fibers of the ascending segment of the palmar aponeurosis and the ones of the dermis. Hematoxylin–eosin 1:100

amount of elastic fibers and consequently have a high degree of elasticity. Another common feature is their involvement in Dupuytren Disease. In contrast, tendons are force-transmitting structures with a low elastic component and do not develop Dupuytren contracture. Figure 9.3 shows the difference in response to load bearing between normal flexor tendons and palmar aponeurosis (Millesi 2012).

Figure 9.3 shows that each tissue type lengthens (strain) moderately under low tensile load (stress). This is referred to as the *toe-in region* of the stress–strain curve. The toe-in region of connective tissues represents tissue lengthening under tension accommodated by the elastic capacity of the tissue. However, beyond this elastic capacity, tissue lengthens less for a given increase in load, and the slope of the stress–strain curve rises abruptly. This segment, between elastic tissue deformation and mechanical tissue failure, is referred to as the *linear region* of the stress–strain

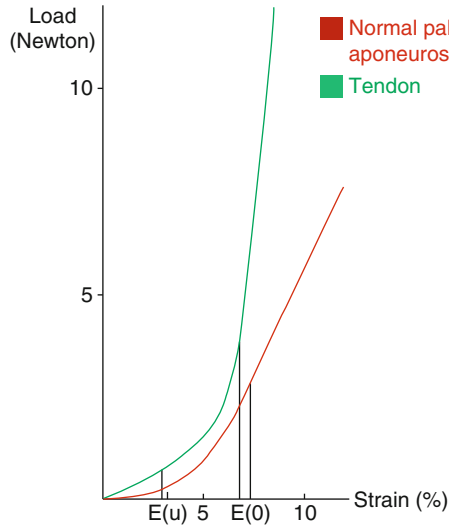


Fig. 9.3 Stress–strain test of flexor tendon and of palmar aponeurosis. Comparing the stress–strain test of fiber bundles of flexor tendon (*green*) and fiber bundles of palmar aponeurosis (*red*). The flexor tendon tissues are more stiff, and the palmar aponeurosis tissues are more elastic (Millesi 2012)

curve. The slope of the linear region reflects tissue stiffness. Figure 9.3 shows that palmar aponeurosis tissue is less stiff than flexor tendon tissue.

Elastic fibers are present in all dense connective tissue, including tendons and ligaments. These elastic fibers have two functions. The first is to recoil collagen fibers back into their resting crimp conformation when stress subsides. The second is mechanical energy storage and release through which tissue stretch and recoil supplement the force of intermittent muscle action. Compared to tendon tissue, the palmar aponeurosis tissue contains more elastic fibers in different arrangement, which may be a reason why the palmar aponeurosis may develop Dupuytren contracture, while tendons do not.

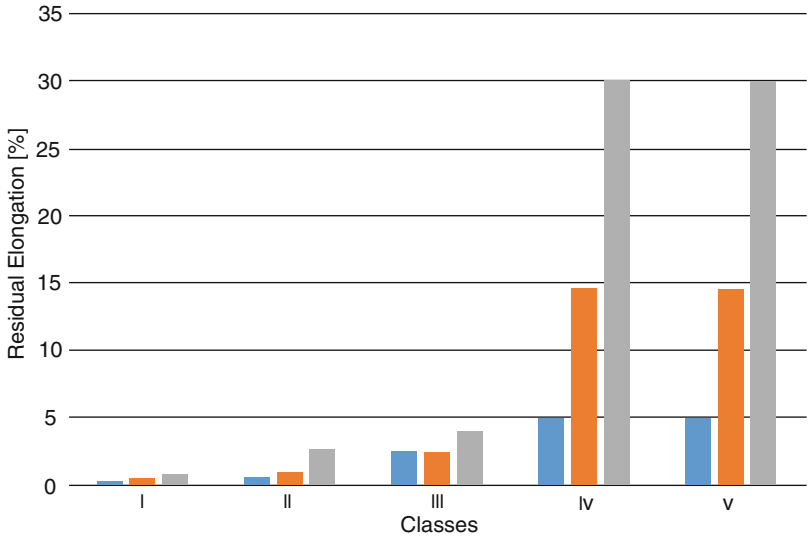
The majority of the body's elastic fibers are created early in life and normally have a low rate of degradation and turnover during one's life span (Sherratt 2009). Their life span may be shorter in the elastic connective tissue and due to genetic factors. Various other conditions may influence the properties of elastic fibers (alcohol, smoking, diabetes mellitus, etc.). Loss or weakness of elastic fibers causes loss of crimp structure, changing the mechanical characteristics of collagen fiber bundles. With loss of recoil and crimp, residual elongation increases (Table 9.1). This mechanical role of elastin is demonstrated by significant increase of the residual elongation of specimens of normal palmar aponeurosis treated with elastase to remove elastin (Reihsner et al. 1991).

9.3 How Does Dupuytren Contracture Start?

The cellular nodule, described by Langhans (1887), is the first stage of Dupuytren contracture (Luck 1959). On average, at least 2.5 years pass from the earliest diagnosis to the earliest surgery (DiBenedetti et al. 2011).

The author performed a unique series of cadaver dissections to define the earliest stages of the onset of Dupuytren contracture. All palmar aponeuroses of all cadavers dissected during one semester at the Department of Anatomy of the University of Vienna were studied by the author for signs of Dupuytren Disease. Specimens with very early, subclinical changes and their gradual transition into the full picture of DC could be studied. These results were compared with surgical specimens after complete fasciectomy containing apart from the contracture bands all stages of beginning DC and also apparently normal segments. The result was that the cellular proliferation is preceded by significant changes of collagen fibers and collagen fiber bundles (Millesi 1959). The most impressive change identified was the loss of the crimp structure (Fig. 9.4). The collagen fiber bundles thicken and fuse partially to form major units, but the original structure can still be recognized (Fig. 9.5). The elastic fibers disappear between the thickened fiber bundles exposed to traction. They survive in transverse fiber bundles of the deep transverse palmar ligament, which never is involved by DC (Fig. 9.6). Elastic fibers of the gliding tissue between the bundles lose their function and can be viewed as collections of deformed remnants of elastic fibers (Fig. 9.7; Millesi 1965).

Table 9.1 Residual elongation



Elongation of 2.5 % (blue), 5 % (orange), and 10 % (gray)
I. Palmar aponeurosis
II. Apparently normal palmar aponeuroses of a patient with DC
III. Thickening of collagen fiber bundles
IV. Contracture bands
V. Advanced contracture bands

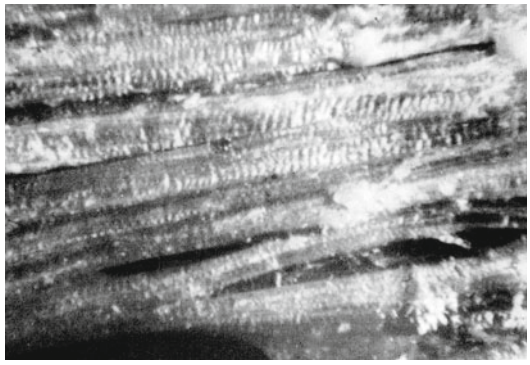


Fig. 9.4 Normal crimp structure. Palmar aponeurosis showing the crimp structure of the normal collagen fiber bundles in relaxed state. Note the rather transparent parallel running fiber bundles. The "cross striation" is caused by the undulated fiber bundles in relaxed state. The light illuminates the height of the waves and causes shadow in between. View by loupe with oblique light, 1: 20

Fig. 9.5 Loss of normal crimp structure in DC. Palmar aponeurosis with initial changes of Dupuytren contracture. The collagen fiber bundles are thicker than in Fig. 9.4. They have lost their transparent appearance and the crimp structure. There is a tendency to fuse with neighboring bundles. View by loupe with oblique light, 1: 20

Very early changes of mechanical properties occur. The stress–strain test of normal tendon shows initially a rise in elongation with little increasing force (the toe-in region) and a steep rise thereafter. When the extending force is removed, de-loading occurs along a different curve as an expression of lost energy (hysteresis). *Residual elongation* is the difference between the starting point of the stress–strain curve and the end point after de-loading (Table 9.2).

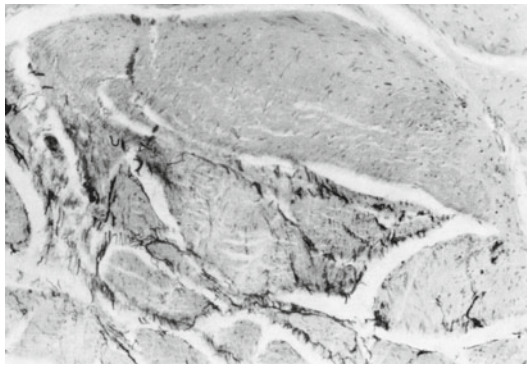


Fig. 9.6 Palmar aponeurosis with early DC. Longitudinal section at the level of the deep transverse ligament. Prantner's elastic stain. At the *upper right part* of Fig. 9.6, a thickened fiber bundle of the palmar aponeurosis is sectioned longitudinally. The thickening, corresponding to an early stage of DC, can clearly be seen. There is no cellular proliferation. There are no elastic fibers. In the *lower left part* of Fig. 9.6, the transversely running collagen fiber bundles of the deep transverse palmar ligament are cut transversely. This ligament is never involved in DC. Here the elastic fibers appear normal and are normally distributed. This supports the concept that the function of the elastic fibers plays a role in the early phase of DC

Residual elongation is the remaining elongation of a specimen that was exposed to a stress–strain test. Initial elongation of up to 3 or 4% occurs with minimal force (the toe-in region). Thereafter, the necessary force rises steeply. After the stress subsides, the specimen retracts again following a different curve. The area between the

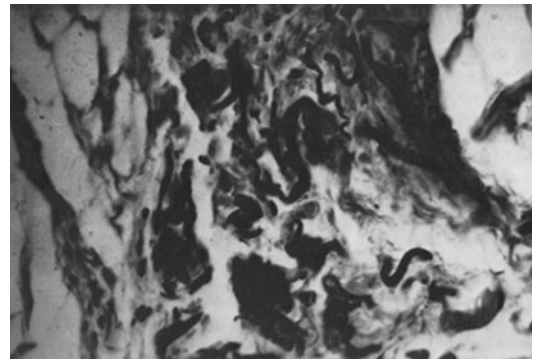
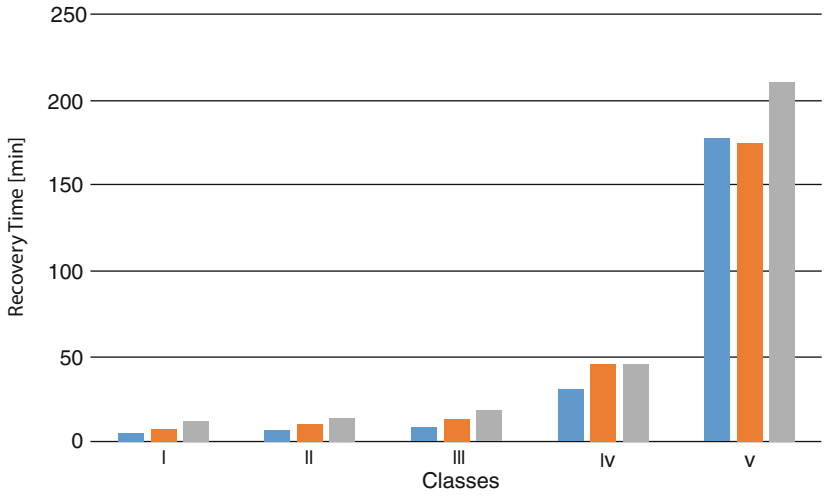


Fig. 9.7 Loose connective tissue between cords of DC. The peri-fascicular and inter-fascicular gliding tissue between the original fiber bundles has been lost. The elastin of the originally high content of elastic fibers cannot be resorbed and remain as fragmented and deformed elastin bodies. Pranter's elastic stain, 1:250

Table 9.2 Recovery time



Elongation of 2.5% (blue), 5% (orange), and 10% (gray)
I. Palmar aponeurosis
II. Apparently normal palmar aponeuroses of a patient with DC
III. Thickening of collagen fiber bundles
IV. Contracture bands
V. Advanced contracture bands

two curves (hysteresis) corresponds to the consumed energy. The original point of the stress curve is never fully reached at the 0-line. The distance between the two points at the baseline is the residual elongation. We have measured the residual elongation after elongation of 2.5, 5, and 10 % (Table 9.1; Millesi et al. 1997).

Repetition of a stress–strain test immediately after the first test produces a different result. The time of rest necessary to get again the original curve is called recovery time. The reason is that the first test initiates an optimizing of the arrangement of fibrils, fibers, and fascicles (warming up in sports). We have measured the recovery time after elongation of 2.5, 5, and 10 % (Table 9.2).

Tissues of palmar aponeurosis affected with DC, harvested and treated in exactly the same way, are characterized by a significantly increased residual elongation. In a macroscopically normal specimen of palmar aponeurosis of a patient with DC at another location, residual elongation was significantly increased if the test was performed with a 10 % elongation. This abnormal residual elongation was not found after elongation by 10 % in similar specimens obtained from patients without DC (Table 9.1). This biomechanical behavior of apparently normal palmar aponeurosis precedes cellular proliferation in Dupuytren Disease.

The basis of the disease may be a genetically defined abnormality of biomechanical behavior. The increased residual elongation of specimens of palmar aponeurosis of patients with DC is also seen after elastase treatment of palmar aponeurosis tissue (Reihsner et al. 1991). This result supports the view that elastic fibers normally play a decisive role in restoring normal tissue length after mechanical strain. In the phase of fiber thickening, before cell proliferation (Table 9.1), the efficiency of the elastic fibers is reduced and residual elongation is increased. The loss of elastin of the specimens results in further increase of residual elongation.

9.4 Pathogenesis and Aetiology

Considering our present knowledge, the conclusion is tempting that DC is related to, or caused by, a deficiency of elasticity in tissues that have special elastic functions. Changes of elastic fibers can explain the changes documented in early stage disease (Millesi 1965). The fact that the prevalence of DC increases with age coincides with known age-related loss of elastic fibers. There is growing interest in the possible role of elastic fibers in Dupuytren pathogenesis (Alfonso-Rodriguez et al. 2014).

9.4.1 Cellular Proliferation

Cellular proliferation is an essential component of the pathogenesis of Dupuytren Disease. But is it really the beginning of the disease? The evidence that it is preceded by earlier pathologic changing of the properties of the collagen fiber bundle suggests that cellular proliferation might be a consequence rather than the root cause of this disease.

Are these early pathological changes of elastic properties induced by heritable genomics, the environment, or both? We know that heritage, age, and environment may contribute to the disease. If the cells are abnormal from birth, we would expect to see Dupuytren Disease in children – but this rarely (if ever) occurs. Yet cumulative environmental influences associated with aging may slowly change the elastic properties of the palmar fascia over time. Those changes, occasionally also combined with traumatic influences, can eventually trigger abnormal cell proliferation in the palmar fascia in adults. Perhaps cells carrying predisposing genetic traits are easier to trigger into hyperproliferation than normal palmar fascia cells. Overall this is still a not fully understood complex process requiring more research into its root causes.

An alternative to this model would be that the cellular proliferation is a separate disease. It could be a tumor-like condition triggered by a preceding disease. If so, we would have to treat two different diseases which are linked together like twins, and we would have to explain the marked differences to other well-known fibromatosis. The early morphologic and the biomechanical changes would remain unexplained.

9.4.2 What Is the Natural Course?

Despite evidence to the contrary (Millesi 1965), a commonly published misconception is that the natural course of Dupuytren Disease is continuous progression (like a malignant tumor) and that successful treatment stops progression. This is certainly not true. Cases of spontaneous regression have been described. In many cases contracture bands can be observed for years without any sign of activity. Such low progression rates may explain differences of gender rates, racial distribution, incidence and prevalence, disease, and contracture. Consider that for patients in Central Europe under treatment for DC, the ratio of male to female patients is 5 to 1. The difference is much less pronounced if in a home for the elderly, all cases with DC including subclinical cases are counted. Japanese surgeons may report that DC is extremely rare, yet in elderly Japanese the frequency of subclinical cases is quite high (Egawa et al. 1985).The same conclusion can be drawn comparing incidence and prevalence (DiBenedetti et al. 2011).

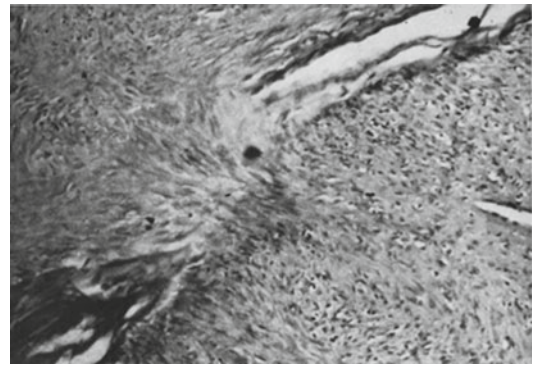


Fig. 9.8 Starting of a cord. Two thickened fiber bundles of a fairly advanced phase of DC with cellular proliferation are still separated by peri-fascicular tissue according to the original bundle structure. In both fiber bundles, cellular proliferation has already replaced the original deposition of collagen. In the center of the figure, the cellular proliferation has already perforated the separating peri-fascicular tissue. At the end of this process, the separating tissue will disappear completely. A large cord without internal structure will be the result. This change of structure also causes changes of the biomechanical behavior (see Tables 9.1 and 9.2). With time the content of cells will be reduced and the content of collagen increased. The end is a scar-like cord, full of collagen and few cells. Hematoxylin and eosin, 1:250

9.4.3 What Are the Activating Factors After Periods of No Proliferation?

In the very early stage, longitudinal traction on the collagen fiber bundles – not softened during the initial phase by the crimp structure – may cause loss of elasticity and thickening by collagen production. The thickened bands are palpable and impede further elongation but do not cause significant contracture. In this phase the stress–strain recovery time (RT) remains low. Fiber bundles thicken, but only to a limited extent. The movement of the fibrils during creep is still limited by the remnants of the fascicular pattern. At this stage, exposure to further mechanical stress causes further thickening.

After cell proliferation the remnants of the original fiber pattern disappears (Fig 9.8). Thick homogenous cords filled with collagen microfibrils are the result. The micro fibrils are now more mobile within the large cord.

Based on these observations, a theory of passive contracture could be as follows: Strong traction may lengthen a cord by movement of the microfibrils. Because the volume of cord tissue is not changed, elongation is compensated by reduction of the transverse diameter. In physics this is called transverse “contraction” in spite of the fact that a true contracting force does not exist. This deformation produces compound force vectors in adjacent tissues which would reestablish the original state. However, the lag of prolonged recovery time (we have measured up to 3 h) can produce an oscillating mechanical feedback loop. This effect can vary enough to give the appearance of a random process. In addition to this, longitudinal traction remains the stimulus for further contracture. It is more active if the cord is longer and spans a wider arch. It loses force beyond certain angles. Usually contracture stops if finger flexion contracture progresses to the point that longitudinal traction on the cord stops, either from intrinsic joint contracture or severe deformity. Activity stops if a cord

is transected and the two stumps spread apart as it could be achieved by fasciotomy. However, after the subcutaneous fasciotomy wound has healed, scar tissue reestablishes continuity, and the stimulating effect of longitudinal traction returns (Millesi 1965), often resulting in recurrent contracture. The effect of fasciotomy could be prolonged by covering the fasciotomy wound by a full thickness skin graft (Armstrong et al. 2000). Recurrences can be slowed but not prevented.

9.4.4 Plantar Aponeurosis

The following argument supports the role of longitudinal traction to initiate and maintain contracture. It is a fact that thick bands at the medial margin of the plantar aponeurosis usually do not produce contractures of the toes. In contrast to the fingers, the metatarsophalangeal joints of the toes are normally in hyperextension. A connection from the plantar aponeurosis to the toes across the connective tissue of the foot does not develop as it does at the hand with the major tendency to flex the MPJ. No longitudinal traction by extending the toes is transferred to the plantar aponeurosis. Consequently, no contracture occurs.

The human plantar aponeurosis is the result of a different development as the ones of the nonhuman primates. The latter have developed the foot to a kind of gripping organ similar to the hand with an opposing thumb and digits in middle position of the tarsophalangeal joints. The plantar aponeurosis is consequently similar to the palmar aponeurosis of nonhuman primates.

The human foot has a completely different development. The foot is not used for gripping but for running. The calcaneus has developed to the dorsal bony support of the foot in an angle to the tibia and fibula. The ventral bony support is provided by the heads of the metatarsal bones, again in an angle to the tibia and fibula. A triangle is formed with the plantar aponeurosis as the hypotenuse. If weight presses the foot to the floor, the triangle widens a bit. The elastic plantar aponeurosis is placed under tension and conserves energy which helps to lift off the foot.

In addition, the plantar aponeurosis stabilizes the skin and prevents tangential motion, similar to the effect of the palmar aponeurosis. A patient that we treated suffered from a congenital absence of the plantar aponeurosis. This patient had extreme difficulties walking barefoot due to the mobility of the plantar skin.

The relation to DC is the fact that the plantar aponeurosis is also a dense elastic tissue. The same is true for Peyronie disease. This answers the initial question 2: *To what extent similar diseases at the plantar aponeurosis (Ledderhose Disease) and at the tunica albuginea (Peyronie disease) are related to Dupuytren Disease and why?*

9.5 Summary

The pathogenesis of DC is more complicated than usually reported. A tumor-like fibroblast proliferation leading to cords with contraction by myofibroblasts does not explain the very early changes, including loss of the elastic fibers and the biomechanical consequences of this. The special elastic properties of the dense elastic tissue complex of the palm, the plantar fascia of the foot, and the tunica albuginea of the penis are the link between Dupuytren, Ledderhose, and Peyronie diseases. In Dupuytren Disease, the loss of elastic properties initiates fibrosis and formation of thick bands, which prevent elongation, but causes little or no contracture. Biomechanically, this stage is characterized by the increase of the residual elongation following tensile stress (Table 9.2). This stage may continue for years, leading to big differences between incidence and prevalence of DC. For so far unknown reasons, a proliferation of fibroblasts originates from perivascular spaces and removes the collagen of the bundle, changing the infrastructure of the bundles (see Fig. 9.8). At the height of the cell proliferation, the whole bundle is full of cells. Such proliferations may occur in the same hand at different times and different locations. New collagen is produced, and eventually the number of cells decreases and a scar-like appearance results. Thick cords develop and undergo contracture if

under tension. At this stage, the mechanical tissue recovery time after is enormously increased (Table 9.2). Contracture progresses until traction on the cord no longer occurs.

Acknowledgments and Conflict of Interest Declaration Figures 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, and 9.8 and Tables 9.1 and 9.2 are being reproduced by permissions of Springer and Thieme Verlag. The author has no conflict of interest to declare.

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Controversy: The Contracture in Dupuytren Disease Is an Active Process

10

Jagdeep Nanchahal and David Izadi

Contents

10.1 Introduction

All cellular processes involve energy expenditure and hence can be considered to be active. These include cell migration, proliferation, matrix deposition and remodelling. In Dupuytren Disease the key cells are the myofibroblasts, which are responsible for matrix deposition and shortening.

10.2 Myofibroblast

10.2.1 The Cell

The hallmark of all fibrotic disorders is the presence of activated myofibroblasts. A myofibroblast is characterised by the presence of α-smooth muscle actin (α-SMA), the contractile element seen in smooth muscle cells, pericytes and myoepithelial cells. However, only myofibroblasts assemble their α-SMA into stress fibres that form the contractile apparatus of the cell. This mechanism is, for example, different from smooth muscle cells, which express the myosin heavy chain (Hinz 2015b), whereas myofibroblasts express non-muscle myosin II (Southern et al 2016). Unlike the relatively short-lived contraction of striated and smooth muscle, myofibroblast contractions tend to be sustained. Some of the earliest work that identified myofibroblasts in granulation tissue characterised their sustained contraction of tissue (Majno et al. 1971).

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10.2.2 Coordinated Activities

Myofibroblasts are also characterised by the presence of specialised junctions that connect them to the matrix and to adjacent myofibroblasts (Follonier Castella et al. 2010; Hinz and Gabbiani 2003). The former are termed fibronexi (Singer et al. 1984; Yannas 1998), and the latter include adherens junctions, mechanosensitive junctions and gap junctions. Adherens junctions are composed of cadherins that extend through the plasma membrane and mediate calcium-dependent intercellular adhesion through homophilic association of their ectodomains (Yap et al. 1997; Follonier Castella et al. 2010). The cadherin receptors associate intracellularly with several structural and signalling proteins, most notably β-catenin, as well as the α-SMA cytoskeleton (Yap et al. 1997). OB cadherin or cadherin 11 predominates in myofibroblasts (Hinz et al. 2004; Verhoekx et al. 2013). Mechanosensitive ion channels open when force is transmitted by an adjacent cell via adherens junctions, allowing an influx of cations such as calcium. Adjacent cells can also communicate directly via gap junctions. Gap junctions are composed of six connexin 43 molecules. Hexamers in adjoining cells make direct contact to allow passage of molecules of up to 1 kDa between cells via hydrophilic channels. We showed that Dupuytren myofibroblasts function as a coordinated cellular syncytium via the 3 types of intercellular junctions (Verhoekx et al. 2013). Inhibition of the intercellular junctions reduced the contractile effect on the matrix by approximately 50 %, and disassembly of the cellular cytoskeleton abolished the remaining 50 %, suggesting the residual activity was due to tension exerted by the individual cells on the matrix via the focal adhesions (Verhoekx et al. 2013).

10.3 Matrix

10.3.1 Deposition, Degradation and Remodelling

Activated myofibroblasts play a prominent role in the secretion of the matrix that accumulates in fibrotic disorders. This includes the collagens as well as a proteoglycans, fibronectins, fibrillins, tenascins and various growth factors and cytokines (Klingberg et al. 2013). Furthermore, the myofibroblasts are highly active in remodelling the matrix, and multiple studies have highlighted aberrations in matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs (TIMPs) in Dupuytren Disease at the mRNA and protein level (Ulrich et al. 2003, 2009; Augoff et al. 2006; Johnston et al. 2007; Ratajczak-Wielgomas et al. 2012). Overall, these data suggest a high turnover state of the matrix, with increased expression of MMP1, MMP2, MMP12, MMP14 (MT1-MMP), TIMPs 1 and 2 and ADAMTS-14. The deposition, degradation and remodelling of the matrix are all processes that require cellular activity.

10.3.2 Contraction by Myofibroblasts

Tomasek et al. (2002) proposed an elegant model of how fibrotic contractures develop as opposed to short-lived muscle contractions. They proposed that myofibroblasts contract the local matrix. The cells then add new matrix components to the shortened framework. The process is repeated by multiple cells such that localised matrix remodelling around multiple groups of cells results in tissue contracture (Fig. 10.1). This process was subsequently likened to a lockstep or ratchet mechanism (Follonier et al. 2008).

10.3.3 Vicious Cycle

A prominent pro-fibrotic cytokine is TGF-β1. It is secreted and resides in the matrix as an inactive form. Traction on the matrix by myofibroblasts liberates active TGF-β1, which can then bind to the cell surface receptors to upregulate transcription of genes associated with fibrosis (Hinz 2015a).

Conclusion

Fibrotic contractures only develop in living tissues, and, as for all other fibrotic contractures (Tomasek et al. 2002), the contracture in Dupuytren Disease that results in flexion

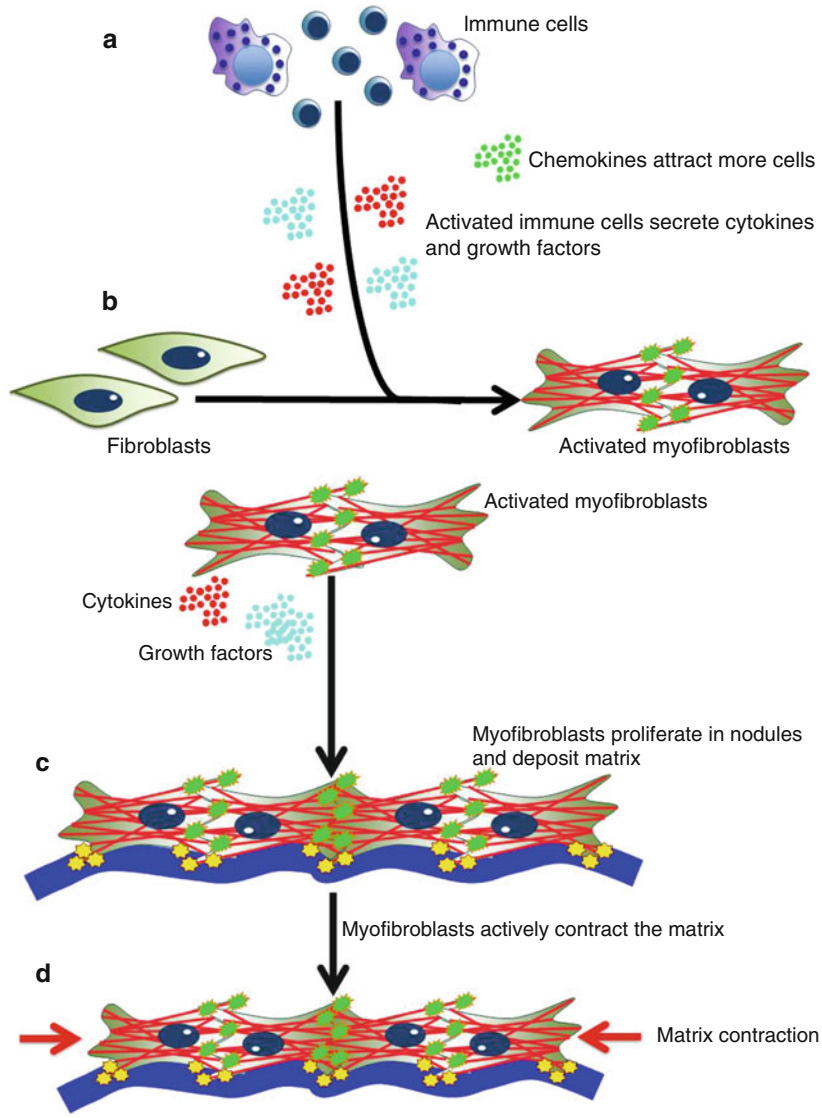

Fig. 10.1 Schematic showing the development of contractures in Dupuytren patients through a series of active processes, involving cell recruitment, cell differentiation, metabolism, cell and matrix contraction, secretion and phagocytosis. (**a**) Resident immune cells in the fascia of genetically susceptible individuals are activated, and more immune cells from the circulation are attracted to the site by locally secreted chemokines. (**b**) The cytokines and growth factors convert the precursor cells into myofibroblasts. (**c**) In the presence of growth factors and cytokines, the myofibroblasts proliferate and secrete matrix components that make up Dupuytren cords. The myofibroblasts communicate with each other through intercellular junctions (*shown in green*) and attach to the matrix via specialist adhesions (*shown in yellow*). (**d**) Through their coordinated actions, groups of myofibroblasts contract the matrix. (**e**) The myofibroblasts remodel the matrix through the action of matrix-degrading enzymes. (**f**) The myofibroblasts secrete further components to augment the shortened matrix. (**g**) Eventually the myofibroblasts disappear and the patient presents with relatively acellular contracted cords of advanced disease

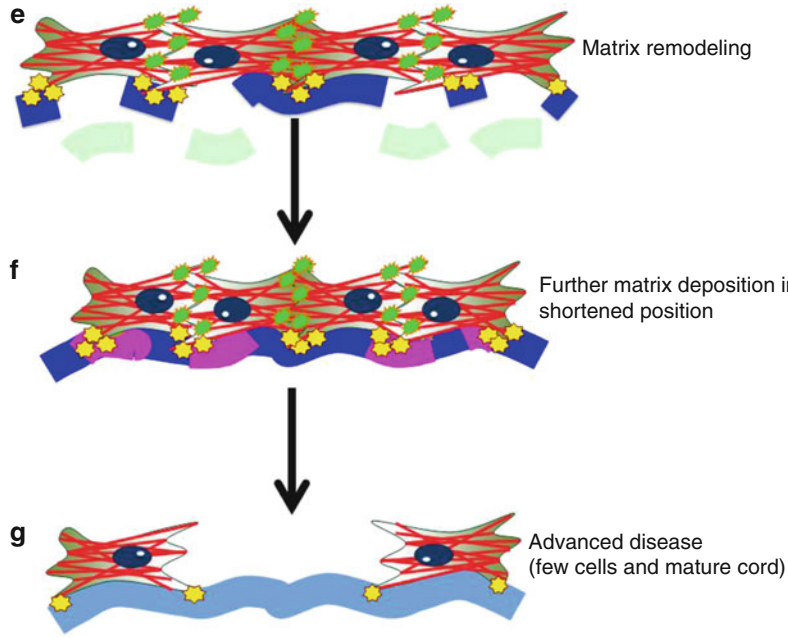

Fig. 10.1 (continued)

deformities of the digits is an active process. All of the following components of the process require cell activity and energy expenditure:

1. Inflammation, which precedes all forms of fibrosis (Wick et al. 2013)
2. Generation of activated myofibroblasts
3. Secretion of matrix components, growth factors and cytokines by the myofibroblasts
4. Contraction of the matrix by the coordinated activity of myofibroblasts
5. Further matrix deposition and remodelling by myofibroblasts

Conflict of Interest JN has received research support and consultation fees and is a shareholder in 180 Therapeutics. IZ has no conflicts of interest.

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Controversy: The Contracture in Dupuytren Disease Is a Passive Process

11

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Contents

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11.1 Introduction

The cellular mechanisms producing Dupuytren contracture are not fully understood. The case is made here that there are two possible mechanisms of myofibroblast-mediated tissue contraction and that Dupuytren contracture is passive, produced by isometric contraction guided by tissue slack rather than an active deformation produced by isotonic contraction. The concept of passive Dupuytren contraction was initially proposed by Meinel in 1994, based on anatomic dissections (Meinel 1994). It remains a useful framework to understand the deformity of Dupuytren contracture (Meinel 2012, 2013) and is consistent with recent studies of myofibroblast mechanobiology.

11.2 Definitions

The terminology of Dupuytren deformity can be confusing, in part because the same words are used to describe different processes occurring on microscopic and macroscopic levels. These terms will be used in this discussion. *Contraction is microscopic*: temporary changes in the shape of a cell or in the arrangements of a cell's attachments to the extracellular matrix. *Isotonic contraction* affects local geometry more than it affects tension of the extracellular matrix. *Isometric con-*

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traction has a greater effect on cell and matrix tension than it does on local geometry. *Contracture is macroscopic*: tissue shortening, the end result of tissue remodeling. *Active contracture* is tissue shortening independent of resting tissue tension. *Passive contracture* is tissue shortening directly guided by posture-related tissue slack. The concept is illustrated in Fig. 11.1.

11.2.1 Active Contracture

One example of active contracture is the end result of *scar contraction*. With one notable exception, scar contraction follows all injuries exceeding a certain threshold of tissue damage (mechanical, burn, radiation, infection, ischemia, or chemical) or in response to spontaneous healing of an open wound. Scar contracture is initiated by cytokines released by cell death and matrix disruption. Products of matrix degradation such as collagen fragments promote myofibroblast differentiation, and tissue stress provokes myofibroblast differentiation and contraction. A full thickness open wound lacks the normal stress shielding of intact dermis, resulting in a uniquely powerful stimulus to myofibroblast differentiation and contraction through a variety of mechanisms, including cell-matrix mechanotransduction, tension-related conformational changes in TGF-β, and others (Hinz 2007; Klingberg et al. 2014). Under maximum stimulation, myofibroblast matrix shortening of an open wound continuously advances the wound edge with velocity as great as one centimeter per month (Castella et al. 2010). Active contraction biology of an open wound continues until the wound is closed, tissue breakdown products are cleared, and matrix tension stabilizes. Although contraction is a cellular process, the matrix plays an important role, as suggested by the fact that freeze injuries, which kill cells with little or no matrix damage, do not contract unless complicated by infection or other injury (Ehrlich and Hembry 1984). Active scar contracture *changes* the posture or geometry of adjacent tissues.

11.2.2 Passive Contracture

For comparison, an example of passive contracture is *post-immobilization proximal interphalangeal joint stiffness in the absence of trauma*. In full extension, normal tendons and ligaments of the finger proximal interphalangeal (PIP) joints are at full length. PIP immobilization in extension may cause joint stiffness but rarely results in contracture. Stiffness is due to binding of gliding surfaces due to loss of normal synovial fluid movement, but the dimensions of the tendons and ligaments are unchanged. After PIP immobilization in extension, recovery of full range of motion is typical. PIP immobilization in flexion is different. The palmar PIP ligament complex and cruciate pulley segments of the flexor tendon sheath are lax in flexion. During prolonged immobilization in flexion, these areas undergo tissue remodeling which removes this position-related palmar slack. Following immobilization in PIP flexion, these structural changes persist, which can produce permanent flexion contracture. This is a common secondary effect of Dupuytren contracture, persisting after release or removal of shortened Dupuytren tissue. Immobilization contracture *maintains* the slack posture or geometry of adjacent tissues.

11.3 Evidence for Passive Contracture

Three clinical observations provide evidence for passive contracture in Dupuytren contracture.

11.3.1 Resting Tissue Laxity

Dupuytren Disease contractures follow the location and direction of resting tissue laxity (Table 11.1). Dupuytren nodules are common in the palmar surfaces of the hand and fingers adjacent to flexion creases (palmar Dupuytren nodules), in the tissues dorsal to the finger joints (Garrod pads), and in the medial border of the plantar fascia in the instep of the foot (Ledderhose

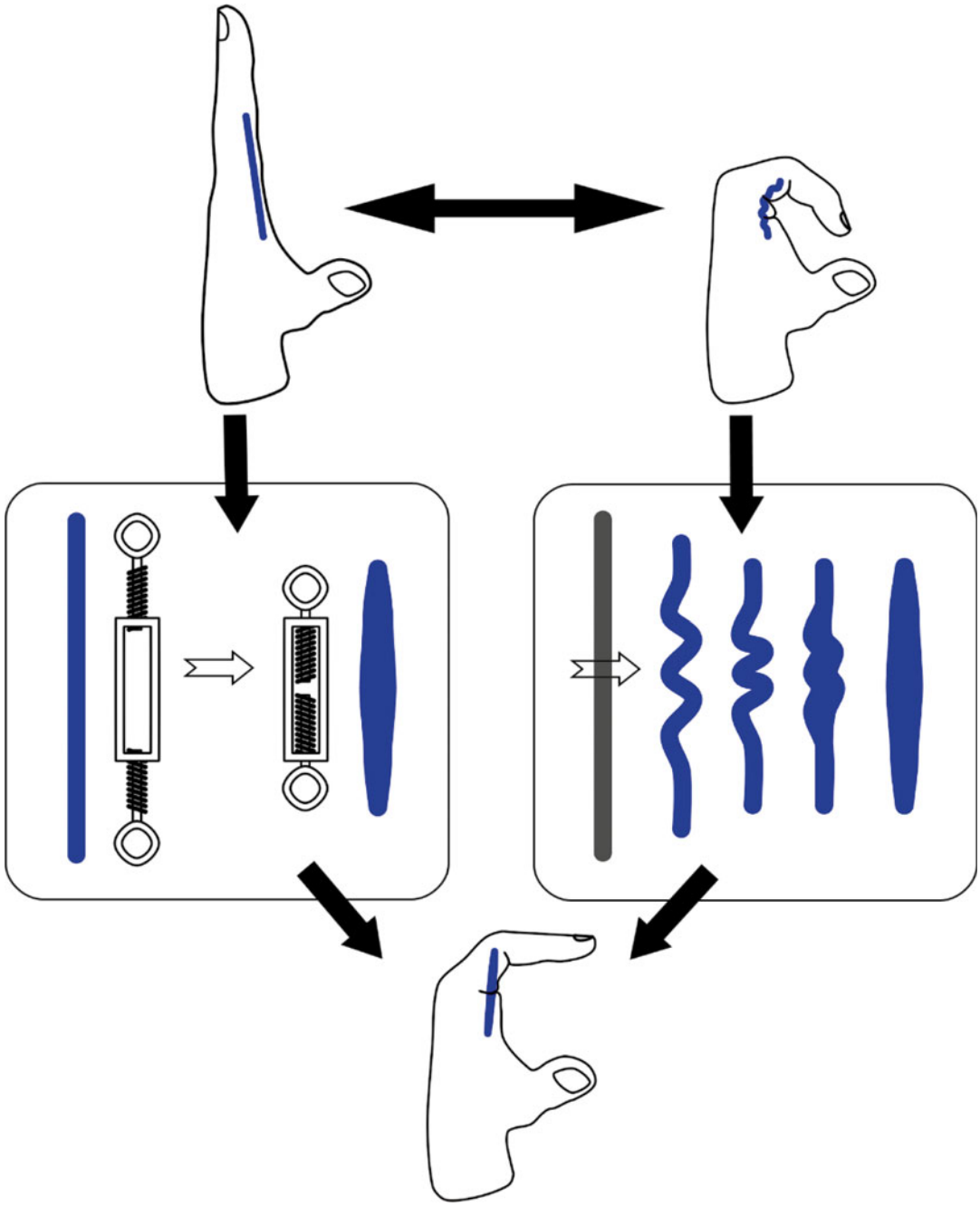

Fig. 11.1 Active versus passive contracture concepts. Comparison of active and passive contracture concepts. The *blue lines* represent fascia and connective tissues in two hypothetical models of Dupuytren contracture. The active contraction model continuously shortens these tissues. The passive contraction model only shortens these tissues when they are lax. *Top*: fascia accommodates full finger flexion and extension by conformational changes similar to folding and unfolding. Fingers rest in flexion. *Left*: *active contracture* concept of tissue shortening. The turnbuckle represents tissue contraction *independent of the posture of the finger. Right*: *passive contracture* concept of tissue remodeling. At rest, *depending on the posture of the finger*, shortening conformational changes from tissue slack are made permanent by tissue remodeling which removes posture-related slack in individual collagen strands. *Bottom*: the end result of each mechanism has the same tethering effect, limiting finger extension

Table 11.1 Dupuytren contractures follow the direction of resting tissue laxity

Nodule location	Resting tension	Contracture?
Palm	*Lax*	*Yes*
Dorsal finger (Garrod)	Tight	No
Plantar (Ledderhose)	Tight	No

Disease). These locations suggest that Dupuytren Disease nodules occur in areas of intermittent longitudinal tissue tension. However, only one of these areas commonly progresses to longitudinal tissue shortening: the palmar areas of the hand and fingers. One possible explanation is that this is the only location where the resting posture results in nodular tissue slack. The finger joints rest in flexion, placing slack in the palmar tissues and removing slack from the dorsal finger tissues. Because of this, Garrod pads do not cause PIP extension contractures – it is not the resting posture. Similarly, the toe metatarsophalangeal joints rest in extension, removing slack from the plantar fascia. Because of this, Ledderhose does not cause plantar flexion contractures – it is not the resting posture. A model of tissue change maintaining tissues at their gross resting length explains these regional differences in contracture risk.

11.3.2 The Timing Is Wrong for a Model of Active Contracture

If the biology were to actually parallel that of wound contraction, Dupuytren tissues could shorten as rapidly as one centimeter per month. At that rate, Dupuytren Disease could progress from nodule to full contracture with fingertip touching the palm in half a year. Clinically, this is extremely rare, if ever. Most Dupuytren contractures progress over the course of many years.

11.3.3 The End Point of Contracture Is Inconsistent with Active Contracture

Active contracture is driven by tissue conditions and continues without stopping until tissues have reached equilibrium. This process is inconsistent with two clinical aspects of Dupuytren contracture. The first is that progression of *Dupuytren contracture is often episodic, separated by long periods of stability*. Scar contracture does not behave this way. The second is that in the absence of additional factors such as spasticity or scarring from trauma or surgery, *severe Dupuytren contracture does not progress past the normal range of motion of affected joints*. Burn scars may pull joints well beyond their normal range, but this is not seen with Dupuytren contracture. One interpretation is that Dupuytren contracture *follows* rather than *leads* joint position. Dupuytren contracture deformity mimics the resting posture of the fingers. This is more consistent with passive contraction than active contraction.

11.4 Cellular Mechanisms of Active Versus Passive Contracture May Differ

In vitro models of myofibroblast tissue remodeling suggest two different overlapping contractile mechanisms, periodic and isometric (Castella et al. 2010) (Fig. 11.2). *Periodic cell contractions* (Fig. 11.3) are controlled by calcium-mediated mechanisms. They are brief, spontaneous, and frequent, occurring about 40 times an hour. They can reposition the location of cell-matrix adhesion complexes on the cell membrane. They are too weak to deform the shape of the cell or matrix but can remove slack from individual collagen strands bound to focal adhesions on the surface of the cell. *Isometric cell contractions* (Fig. 11.4) are mediated by Rho kinase mechanisms. They are sustained, lasting hours. They are a thousand times more strong than periodic contraction and strong enough to deform the myofibroblast and to actively deform the surrounding matrix through attachments of multiple collagen strands to large adhesion complexes on the cell surface. This terminology can be confusing. In this context, the process referred to as isometric cell contraction produces a sustained increase in matrix tension, but because it is potentially strong enough to deform the matrix, the action is not purely

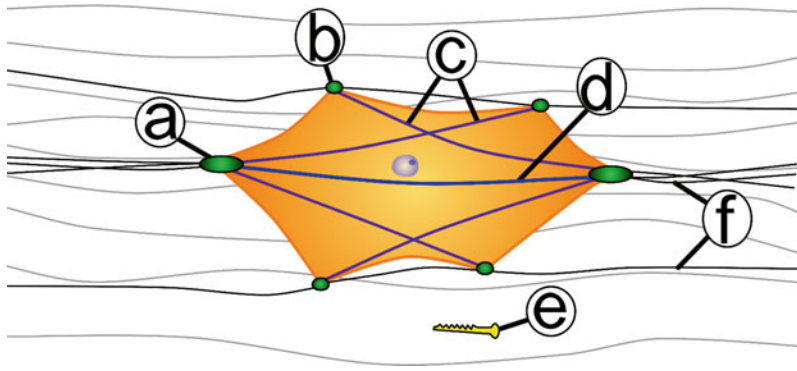

Fig. 11.2 Components of the myofibroblast and extracellular matrix. The central structure is a myofibroblast. *a* Large adhesion complex spanning the cell membrane, attached to both extracellular and intracellular stress fibrils. *b* Focal adhesion spanning the cell membrane, attached to both extracellular matrix fibrils and subcellular stress fibrils. *c* Subcellular stress fibrils responsible for periodic contraction. *d* Global stress fibrils responsible for isometric contraction. *e* Extracellular matrix proteolytic enzyme and cross-linker which joins adjacent collagen strands. *f* Extracellular matrix collagen fibrils

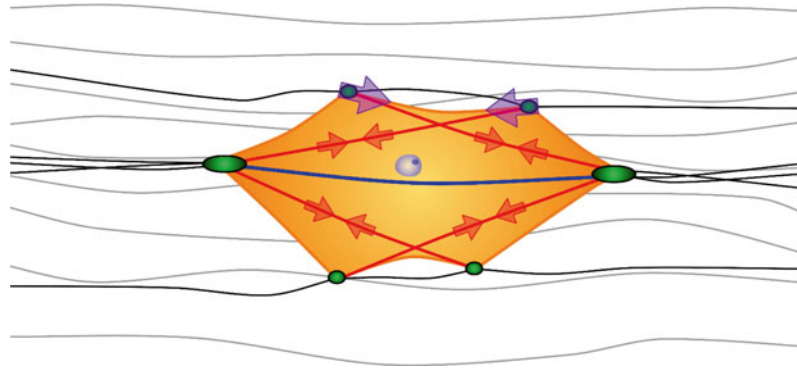

Fig. 11.3 Periodic myofibroblast contraction. In periodic myofibroblast contraction, subcellular stress fibrils shorten, pulling on focal adhesions in the cell membrane. Periodic contractions are not strong enough to deform the shape of the myofibroblast but can move the location of move focal adhesions. Further legend details: see Fig. 11.2

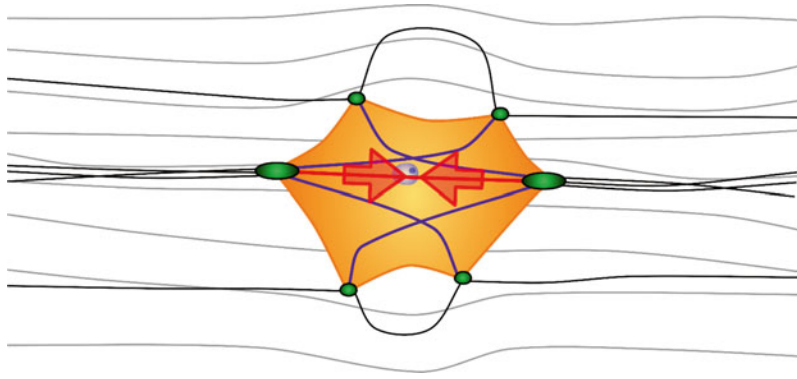

Fig. 11.4 Isometric myofibroblast contraction. In isometric myofibroblast contraction, global stress fibrils shorten, pulling on large adhesion complexes in the cell membrane. Isometric contractions are strong enough to deform the myofibroblast and the surrounding matrix. These strong, sustained contractions tighten matrix strands in line with large adhesion complexes but produce slack in adjacent parallel matrix attached to focal adhesions

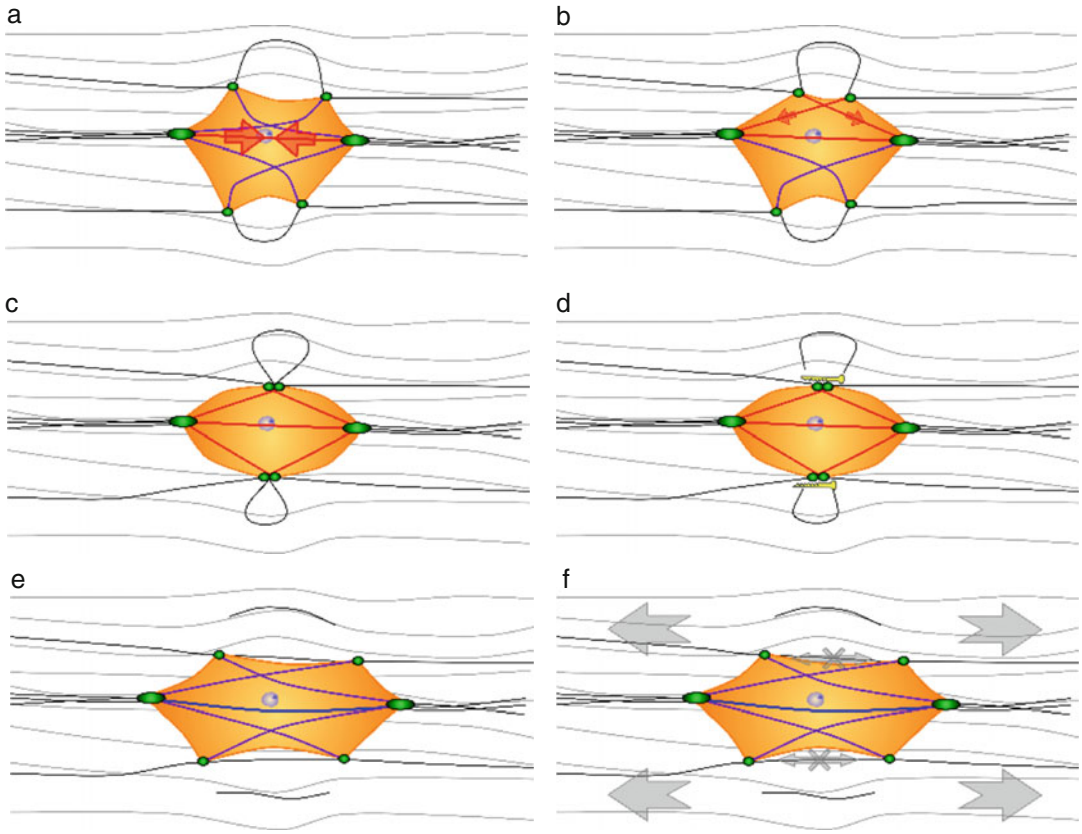

Fig. 11.5 Mechanism of active contracture. Active contractures result from a "lockstep" mechanism. (**a**) Isometric contraction deforms the matrix, tensioning collagen strands at each end of the myofibroblast and creating slack in strands in each side of the cell. (**b**, **c**) Periodic contractions remove collagen strand slack beyond the cell, creating collagen strand loops on the side of the cell. (**d**) While in this position, extracellular proteolytic enzymes and cross-linkers remove divide collagen loops and join segment ends. (**e**) Isometric contractions end, and the cell shape re-equilibrates. (**f**) The process *changes* the tissue posture. Newly shortened collagen strands sustain the matrix deformity created by active cell contraction

isometric. The effect of periodic contractions on individual collagen strands might be considered isotonic because it moves segments of individual lax collagen strands without affecting the overall matrix tension.

11.4.1 A Potential Mechanism of Active Contraction

In wound contracture, both mechanisms may work together in a ratcheting or "lockstep" fashion (Castella et al. 2010). Based on *in vitro* cell culture models, the hypothetical scenario illustrated in Fig. 11.5 can be imagined. The matrix is deformed by isometric cell contractions, producing and maintaining slack in collagen strands adjacent to the myofibroblast. While in this position, periodic contractions act to remove slack from collagen strands, forming collagen loops. This allows extracellular proteolytic and cross-linking enzymes to act, trimming off the redundant collagen loops and joining the freshly cut ends of the strands. The end result is shortening of individual collagen strands, which can then stress shield the myofibroblast from tension on the matrix. This process, occurring throughout the myofibroblast-populated tissues, produces active contracture because it *changes* the initial tissue length.

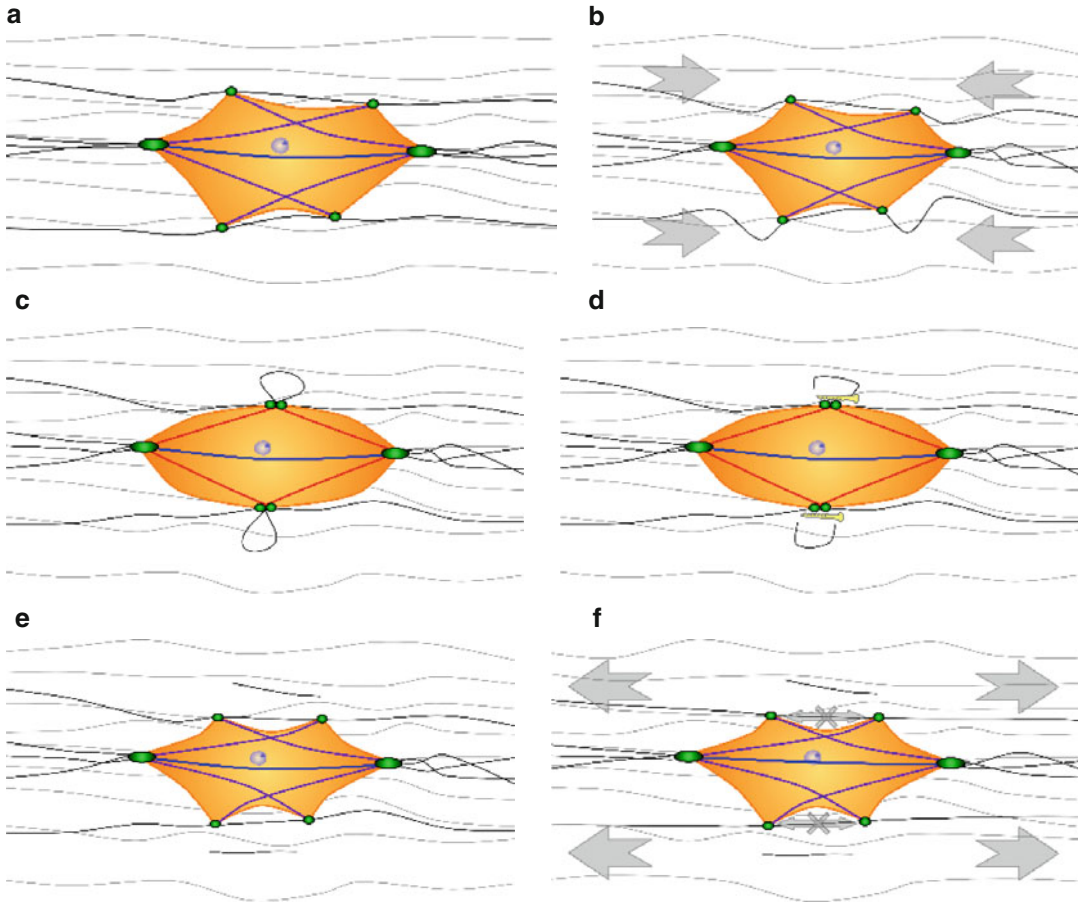

Fig. 11.6 Mechanism of passive contracture. In this hypothetical model of passive contractures, collagen strand slack is produced by joint position rather than isometric cell contraction. (**a**, **b**) Joint position creates generalized slack in the matrix. (**c**) Periodic contractions remove collagen strand slack beyond the cell, creating collagen strand loops. (**d**) While in this position, extracellular proteolytic enzymes and cross-linkers remove divide collagen loops and join segment ends. (**e**) The cell shape re-equilibrates. (**f**) The newly shortened collagen strands *maintain* tissue posture created by joint position

11.4.2 A Potential Mechanism of Passive Contraction

A hypothetical variation of *this process could explain passive contraction* (Fig. 11.6). In this theoretical scenario, a resting position which produces slack in the matrix would allow periodic contraction and extracellular cross-linking to shorten collagen strands simply by removing slack. The result of tissue remodeling would restore the matrix to a normal baseline tension rather than actively deforming the matrix. This process is passive contraction because it *maintains* an existing tissue posture.

11.5 Is This Distinction Important?

Both hypothetical processes involve myofibroblast contraction, and the end result is the same. Is the distinction important? The answer is yes: this is important information for the ongoing search for better treatment options.

If the mechanism is passive contracture and if the basis is periodic contraction, that means that pharmacologic intervention could selectively target calcium-mediated periodic contraction rather than targeting myofibroblasts or myofibroblast contraction as a whole.

This could explain why continuous extension splinting for Dupuytren contracture has shown positive results but intermittent splinting has not. If periodic contraction is essentially continuous (every two minutes), then even short periods relaxing out of the splint could result in contracture.

Both mechanisms may play a role. Hemosiderin deposits in Dupuytren tissues (Larsen et al. 1960) in the absence of known trauma may be due to traumatic effects of strenuous hand use and may cross the tissue threshold for triggering a wound healing type of cellular response. The relative contribution of both mechanisms might explain variability in disease aggressiveness and rates of contracture progression. Mild Dupuytren Disease might only involve periodic contraction; aggressive Dupuytren Disease might also involve some degree of isometric contraction. Biomarkers of the biologic mechanisms of these two processes could result in individualized treatment of different subgroups of disease.

11.6 Summary

Cellular mechanisms directing tissue remodeling of Dupuytren contracture are complex. In some ways, Dupuytren contracture parallels the active contracture of wound healing. However, the rate, variability, and end point of Dupuytren contracture are not easily explained by the wound healing model. In other ways, Dupuytren contracture parallels the passive contracture of atraumatic post-immobilization PIP joint stiffness. Based on models derived from cell culture, the author hypothesizes that these discrepancies may be due to selective involvement of periodic myofibroblast contraction.

Conflict of Interest Declaration The author has no conflict of interest to declare.

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Part III

Genetics and Associations

Dominic Furniss and Hans Hennies,
supported by Paul Werker

Human Genetic Studies of Dupuytren Disease: A Primer

12

Roel A. Ophoff

Contents

12.1 A Simple Principle of Human Genetic Studies

Human genetics is the scientific study of heredity as it occurs in human beings. The value of human genetics lies in the fact that it addresses the issue of causality. Whenever we study biology and observe a phenomenon, for example, a behavioral trait or a disorder that may be life threatening such as Huntington's disease, we may be able to identify a biological hallmark linked to the trait of interest. But simply the fact that there is a biological observation in a group of patients does not mean that this is causing the disease. First, we need to establish that the biological marker is truly linked with the disease, and, secondly, we need to find out whether the biomarker is causing the disease or a secondary effect of having the disease. The beauty of human genetics is that it provides the tools to answer both of these questions and aims to identify the genetic origin of molecular pathways and mechanisms resulting in a specific and individual observable trait, also called a *phenotype*.

The observation that individual traits are passed down through from generation to generation is not new. As long as humans have habited the earth, they have observed similarities and dissimilarities between parents and children, between peoples from different regions or continents. We have records of Plato's writing almost 2,500 years ago (in *Politikos*) where he explains in detail the task of carefully selecting spouses to reproduce children who will develop into bodily and ethically eminent personalities. We can easily dismiss this as a bad example of the earliest eugenics movement and not taking into account the effect of nurture on human beings, but he must have observed a connection between parents and offspring, the inher-

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ited features that impact our physical appearance and our behavioral features. In today's world, the observations are the same, but now we have the knowledge and the tools to specifically study the inheritance of phenotypes and identify the causal relationship between genotype (genetic variation) and phenotype. And this is a simple outline, a principle of human genetic studies (Fig. 12.1). It is significant, because identification of genes involved in disease gives us direction for studying the underlying molecular mechanisms, which in turn will hopefully result in discovery of new therapeutic targets. In short, genetic research is important for discovery of new and improvement of existing treatment of disease.

12.2 Dupuytren Disease as Genetic Trait

Studying the genetic basis of Dupuytren Disease is no different from studying the genetics of other human disorders. First of all, it requires a proper understanding of the clinical manifestations. A proper diagnosis is the foundation of a good human genetic study of a disorder; without this, a study is doomed to fail. A trained physician can readily make the Dupuytren diagnosis. The disease is a benign, chronic, slowly progressive disease affecting the hands. There is accumulation of fibrous tissue beneath the skin of the palm. This tissue shrinks along its length, pulling the fingers into a permanently bent position. Over time, Dupuytren contracture progresses toward a crippling deformity.

In addition to a proper diagnosis, for genetic studies we need to know more about the incidence of the disease, the age of onset, gender differences, and if there are known environmental risk factors for developing Dupuytren Disease. It would be helpful if tools are available to quantify disease severity or understand if there are other disorders that are comorbid with Dupuytren Disease. The big question for genetic studies, however, is the issue of *heritability*. Is there evidence that genetic factors do contribute to the disease? The measure to which extent genetic variation can explain phenotypic variation is captured by the heritability estimate. *Heritability* is a statistical measure to explain how much of the variation observed in a phenotype in a population is due to genetic variation in that population. A simple approach is to examine the familial occurrence and inheritance of Dupuytren Disease in order to get taste of the genetic contribution.

Dupuytren Disease has repeatedly been observed and described to occur in large families across different generation. The first substantial evidence that familial Dupuytren Disease may be a Mendelian trait, i.e., caused by a single genetic factor, transmitted from generation to generation in a pedigree, comes from a study a decade ago (Hu et al. 2005). A genetic linkage study was performed in a large Swedish family with

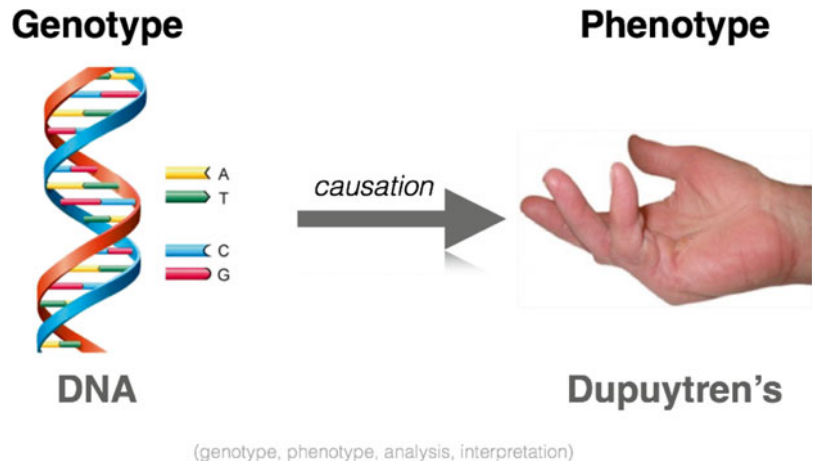

Fig. 12.1 From genotype to phenotype. Human genetic studies of Dupuytren Disease aim to identify the underlying genetic variation (genotype) contributing to the etiology of the disease (phenotype). The disease etiology is likely complex and involves both genetic and nongenetic factors

Dupuytren Disease, resulting in the identification of a genetic disease locus on the long arm of chromosome 16. A genetic locus is a specific region on a chromosome and may contain multiple genes. Even though there was (and still is) no known gene with a mutation causing Dupuytren Disease, the genetic evidence showed that in this pedigree, Dupuytren Disease is inherited as an autosomal dominant trait.

Another important contribution to our understanding of the role of genetic factors and Dupuytren Disease came from a recent study by Becker et al. (2015). They examined a possible link between family history and disease severity of Dupuytren Disease. Individuals undergoing the first surgery for Dupuytren contracture were recruited ($n=801$) without prior selection for family history. The mean age at first surgery was 59.0 ± 12.2 years of age with a range 22–87 years. Almost 40 % of probands reported a family history of the disease with a first-degree relative (i.e., parents or siblings) being affected. However, family history of the disease had the strongest effect on the age of first surgery. Affected individuals with a positive family history were on average 5.2 years younger than patients without known family history, a highly significant difference ($p=6.7E{-}08$)[2]. They also observed that the percentage of familial cases decreased with age of onset from 55 % in the 40–49 age category to 17 % for age 80 or older. Even though this study is not a population-based analysis and may be biased toward the most severe cases of DD, the results strongly suggest that a positive family history of the disease is the most prominent risk factor for surgical intervention at an earlier age.

Even though these studies point specifically toward a genetic contribution to disease, the question of heritability remained largely unanswered – until earlier this year. Larsen and colleagues performed the largest twin study of Dupuytren Disease thus far in a population-based twin registry in Denmark (Larsen et al. 2015). The size and scope of the study with >30,000 twins in the general population make this study very valuable for estimating the heritability and population prevalence of Dupuytren Disease. The difference in concordance rates of Dupuytren Disease in monozygotic and dizygotic twins yielded a heritability estimate of approximately 80 % with a prevalence of 0.6 % in the general population (Larsen et al. 2015). The high heritability means that much (but not all) of Dupuytren Disease in the population is due to genetic variation among individuals in that population. It does not necessarily mean that the genetic basis of the disease is simple, however.

These three studies (among some others) show that Dupuytren Disease is a highly heritable trait in which genetic factors are likely to play a role in disease severity. It also leaves room for other, nongenetic factors, such as environmental exposures to contribute as well. Sometimes Dupuytren Disease can manifest itself as a familial disorder inherited in a Mendelian fashion, as seen in the large Swedish family described above. This, however, is rarely the case. The emerging picture of the genetic architecture of Dupuytren Disease is very similar to other human complex traits in which there is a large contribution of many different genetic factors to the genetic risk of the disease (i.e., polygenicity), mixed with a smaller group of monogenic familial forms of the trait.

12.3 Genome-Wide Association Study of Dupuytren Disease

Even though the genetic evidence was limited a few years ago, we embarked on a genome-wide association study (GWAS) of Dupuytren Disease through a large collaborative effort (Dolmans et al. 2011). The purpose of a GWAS is to identify common risk alleles throughout the human genome contributing to a phenotype. Hundreds of thousands of locations in the genome are each examined for a possible link with disease. Success of a GWAS is largely dependent on sample size of the study since most common risk alleles have only a very modest effect on disease risk. To our surprise, we observed strong evidence of genetic risk factors for Dupuytren Disease, even though the discovery sample included <1,000 patients (Table 12.1). Probably the most exciting observation was that many of the nine loci that we identified contained genes known to be involved

in Wnt signaling (Dolmans et al. 2011), pointing to a biological mechanism that is causally involved in the etiology of Dupuytren Disease. Wnt signaling is known to regulate the proliferation and differentiation of fibroblasts in both cancer and fibromatosis; the involvement of the Wnt signaling pathway in the pathogenesis of Dupuytren Disease is consistent with features of the disease and with established aspects of Wnt signaling. The first large-scale genetic study of Dupuytren Disease turned out to be very successful.

But does this mean that we can mop the floors and close the books and go home because all is known about Dupuytren Disease? No, this is clearly not the case. Genome-wide genotype data of Dupuytren Disease can be used to estimate the proportion of phenotypic variance explained by common alleles (i.e., single nucleotide polymorphisms, SNPs) and to better understand the genetic architecture of Dupuytren Disease as complex trait. Approaches to examine polygenic risk scores from GWAS for complex traits were first proposed for schizophrenia and bipolar disorder (International Schizophrenia Consortium et al. 2009). There is a substantial polygenic contribution to complex traits, and risk alleles are enriched among SNPs selected even for marginal evidence for association from GWAS studies. We used the polygenic score analysis to examine the extent to which the same model can be applied to Dupuytren Disease. We used half of the genome-wide genotyped sample of 856 cases and 2,836 controls as discovery and the other half as target to examine polygenicity. The analysis showed that common alleles may explain up to 14 % of the disease variance, while the nine associated alleles (from the GWAS) account for <2 % of the phenotypic variance. Another common tool used for examining the heritability explained by SNPs with common alleles is GCTA (Yang et al. 2011, 2014). When applied to the overall discovery panel of 856 cases and 2836 control subjects, GCTA estimates the genetic variance (Vg) at 0.163 with standard error (SE) of 0.0136, which is fully in line with the results of the polygenic risk score analysis. While common alleles explain a significant fraction of the overall estimated heritability of Dupuytren Disease (~20 % of total heritability), our results also imply that other types of genetic variation including rare coding variants are likely to play an important role in the disease. The identification of these rare coding variants may require family-based studies, which is a different approach than GWAS.

So instead of mopping the floors to clear out the room, if we are serious about understanding the genetic basis of Dupuytren Disease, we should first aim to expand the GWAS efforts to include much larger sample size for comprehensive discoveries. Other traits report GWAS studies of well over 10,000 patients or even 200,000 subjects (Wood et al. 2014; Schizophrenia Working Group 2014) and are leading the way of genetic discoveries. The road to success for Dupuytren Disease is no different. The second observation is that other types of genetic variation must also contribute to the genetic architecture of disease susceptibility. Only a few years ago, it was first observed how abundant rare coding variations are in human genome, many of which are predicted to be deleterious with likely relevance to understanding disease risk (Nelson et al. 2012). It will take time and effort to fully decipher the genetic architecture of Dupuytren Disease susceptibility, perhaps ranging from polygenic trait in many to Mendelian disorder in a subset of pedigrees. The recent advances in genomic technologies, especially in high-throughput sequencing, provide us with a unique opportunity to identify the genetic origins of Dupuytren Disease.

Conclusions

The evidence is solid that Dupuytren Disease is a highly heritable trait and we already have discovered several genetic factors that play a key role in disease susceptibility. If the initial, relatively small GWAS study was any indicator of success, we have high expectations for future discoveries knowing that larger GWAS efforts are being prepared and are underway. It gives us hope that new therapeutic targets will be discovered and effective ways of prevention and treatment will be developed. This is the best of times for genetic studies of Dupuytren Disease.

Table 12.1 Results of a GWAS study identifying nine different loci

Chr	SNP	Position (bp)	Minor allele	P_{GWAS} 856 cases, 2,836 controls	$P_{follow\text{-}up}$ 1,365 cases, 8,445 controls	P_{meta} 2,325 cases, 11,562 controls	OR (95 % CI)	Nearby RefSeq genes
1	rs7524102	22,571,034	G	2.9×10^{-5}	1.0×10^{-4}	$\mathbf{2.8\times10^{-9}}$	1.28 (1.17–1.41)	*WNT4*
7	rs16879765	37,955,620	A	$\mathbf{1.9\times10^{-16}}$	$\mathbf{2.0\times10^{-22}}$	$\mathbf{5.6\times10^{-39}}$	1.98 (1.78–2.18)	*EPDR1, SFRP4*
7	rs1668357	37,970,931	C	$\mathbf{9.5\times10^{-12}}$	–	–	–	
7	rs4730775	116,704,354	A	4.7×10^{-5}	3.7×10^{-4}	$\mathbf{3.0\times10^{-8}}$	0.83 (0.77–0.88)	*WNT2*
8	rs611744	109,297,184	G	4.4×10^{-5}	$\mathbf{7.0\times10^{-11}}$	$\mathbf{7.9\times10^{-15}}$	0.75 (0.70–0.81)	*EIF3E, RSPO2*
8	rs2912522	70,154,934	G	6.3×10^{-8}	3.0×10^{-6}	$\mathbf{2.0\times10^{-13}}$	0.72 (0.66–0.78)	*C8orf34, SULF1*
9	rs10809642	1,189,448	A	2.6×10^{-5}	6.9×10^{-4}	$\mathbf{1.2\times10^{-8}}$	1.35 (1.19–1.53)	*DMRT2*
9	rs10809650	1,192,371	G	1.4×10^{-4}	4.5×10^{-5}	$\mathbf{6.2\times10^{-9}}$	0.80 (0.74–0.88)	
19	rs11672517	62,370,006	A	$\mathbf{2.8\times10^{-8}}$	2.7×10^{-6}	$\mathbf{6.8\times10^{-14}}$	1.34 (1.25–1.45)	*DUXA, ZNF264*
20	rs8124695	38,461,850	A	4.9×10^{-7}	8.8×10^{-4}	$\mathbf{7.6\times10^{-10}}$	1.48 (1.30–1.68)	*SNORD112, MAFB*
22	rs8140558	44,818,937	G	$\mathbf{1.5\times10^{-11}}$	$3.8\times\mathbf{10^{-11}}$	$\mathbf{1.2\times10^{-22}}$	1.39 (1.30–1.48)	*WNT7B*
22	rs6519955	44,800,506	A	$\mathbf{2.8\times10^{-13}}$	$\mathbf{1.7\times10^{-19}}$	$\mathbf{3.2\times10^{-33}}$	1.54 (1.44–1.65)	

Results of 12 SNPs representing 9 different loci with position according to build 36.3, odds ratios from the combined dataset with 95 % confidence intervals (CI). Results meeting the significance threshold ($P<5.0\times10^{-8}$) for genome-wide association are shown in bold. SNP is single nucleotide polymorphism (Dolmans et al. 2011)

Conflict of Interest Declaration The author declares that there is no conflict of interest.

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13 Network Analysis and Fine-Mapping GWAS Loci to Identify Genes and Functional Variants Involved in the Development of Dupuytren Disease

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Contents

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13.1 Introduction

Many DD patients have a positive family history, and genetic factors play a far greater role in the etiology of this disease than is often acknowledged. In 1963, Ling already showed that the rate of patients with a positive family history increased from 16 % reported by the patients themselves to 68 % when the patient's relatives were examined by the author (Ling 1963). Studies have determined varying family predisposition rates in patients, between 12.5 and 44 % (Brenner et al. 2001; Coert et al. 2006; Early 1962; Hakstian 1966; Hindocha et al. 2006a, b; Lanting et al. 2013; Makela et al. 1991). The sibling recurrence risk λ_s has been determined as 2.9 based on a prevalence of 3.5 % in north-western England (Capstick et al. 2013; Hindocha et al. 2006a). We have shown that DD patients who had a known family history for this disease are significantly younger at the time of first surgery (Becker et al. 2015). Moreover, a positive family history had a

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far greater influence on the mean age of first surgery than other risk factors, namely, heavy smoking. We clearly showed in this study that a positive family history, and with it the underlying genetic risk factors, strongly contributes to disease severity (time of first surgical intervention). In a recent population-based twin study, the heritability of DD was calculated to be 80 % (Larsen et al. 2015). Therefore we aim to identify the causal variants in the genome to understanding the genetic basis of this multifactorial disease.

13.2 Previous GWAS Findings

The first GWAS in DD (Dolmans et al. 2011) identified nine genomic loci associated with this disease on genome-wide significant level (p-value $< 5 * 10^{-8}$). Six of these nine loci harbor one gene each that codes for an upstream modulator of the Wnt signaling pathway, e.g., Wnt ligands or inhibitors. This intriguing overrepresentation of Wnt signaling-related genes in the GWAS loci led to the first valuable insight into the possible genetic factors underlying DD. None of these genes have so far been further investigated as the true culprit at a given loci. The complex nature of common diseases makes it a difficult task to identify truly causative genetic variants by linking them to the disease phenotype. This is a well-known problem in complex genetic diseases and presents one of the major challenges of our age.

The majority of GWAS loci that have been identified for complex diseases fall outside of coding genes, and they are supposed to reflect alterations in regulatory features (Schaub et al. 2012). Many of these regulatory effects will be small and difficult to detect individually (Civelek and Lusis 2014). On top of that, GWASs for common, complex diseases (or traits) only explain a small proportion of the genetic basis, and a lot true positives may be hidden in the statistical noise produced by GWAS. This necessitates a systems approach to analyze the pathways and networks involved in DD. In particular network modeling may help to uncover relationships between genes from top GWAS loci, allowing for the inclusion of susceptibility loci with more subtle effects and increasing statistical power to detect them as they are viewed in context of each other.

13.3 Network Analysis

Pathway and network analysis have been extensively used in the analysis of expression data. But they are also useful tools to investigate complex genetic diseases. In complex genetic diseases, different genetic variants within an individual and different genetic variants between individuals contribute to the disease. Genetic variants can act additively and in concert with environmental factors. The same genetic variant in two individuals does not necessarily lead to the disease in both individuals, depending on the genomic background of each individual and the environment the individual was exposed to. Individual genetic variants in complex diseases can cover the whole spectrum of pathogenicity from fully penetrant to slight effects. By design only few of these variants are picked up by GWAS because the multiple testing of thousands of variants (SNPs, markers) requires a strict significance threshold, in order to reduce the number of false positive findings. Consequently only the very top loci are considered in a traditional GWAS approach. But although the genetic basis of a complex disease can be spread out over many genetic loci and genes, these genetic alterations are not randomly distributed but affect a limited number of cellular functions and pathways. This consideration makes it possible to search for functional connections between genes in GWAS loci. In contrast to pathway analysis, network analysis does not require prior knowledge about the function of a gene product or its affiliation to a pathway but relies on a network constructed from protein-protein interaction (PPI) data. The nature of the PPI data can either be physical interactions, classically generated by yeast two-hybrid screens, or other data sources, e.g., co-expression data. A network in this context constitutes interaction data consisting of molecules (e.g., proteins), termed nodes, and their relationships with each other (e.g., physical

interactions, co-expression), termed edges. The aim in network analysis of GWAS data is to identify modules – groups of connected proteins/genes that share characteristics under study – that are enriched in small *p*-values. In this process GWAS data can be integrated with whole transcriptome expression data, for instance, for the disease tissue. Considering genes that are co-expressed in the affected tissue increases the power to detect true associations.

As a complex disease, DD is well suited for a network-based approach (Fig. 13.1). DD has a strong genetic basis, disease tissue and healthy tissue are readily accessible, and some prior information about pathways likely involved in the development of this disease is available (in particular Wnt signaling but other pathways may also be similarly important). Moreover, the phenotype is clearly defined, although the severity of the disease differs between individuals.

13.3.1 Network Analysis Workflow

In the first step SNP-based *p*-values are translated into gene-based *p*-values. For this, SNPs must be assigned to genes. The simplest method to do this is to define a window around each gene and assign all SNPs within this window to this gene. But this is no trivial task as SNPs not necessarily act on the nearest gene and long-range interactions are possible. We used the software VEGAS2 (Mishra and Macgregor 2014), which also takes into account linkage information (e.g., from the 1000 Genomes Project reference population) and gene sizes. VEGAS2 combines the test statistics of all SNPs within ±50 kb of each gene. Based on SNP association *p*-values, the software calculates empirical gene-based *p*-values by a simulation procedure.

The next step is to search for modules enriched in small *p*-values within a protein-protein interaction (PPI) dataset. The assumption behind is that in complex genetic settings, many different variants affecting several different genes may contribute to the disease, but these genes are assumed to act in a limited number of pathways or cellular functions. Because of the limited number of affected pathways/cellular functions, truly associated genes are expected to be more functionally connected to each other than random genes. The search for modules instead of individual genes increases statistical power since association does not rely on individual genes but a module of functionally connected genes.

To further increase the power to detect true associations in the statistical noise of GWAS, one can combine the GWAS data with tissue-specific whole-genome transcription data by considering only genes that are expressed or co-expressed in the tissue of interest when searching for connections between genes with small *p*-values.

Network analysis results in lists of genes. The next logical step to do is to look for enrichment of functional annotations in these lists of genes (e.g., canonical pathways or gene ontology (GO) terms). Although the function of all genes in a sub-network may not be known, this constitutes the first insight into which pathways may be affected by genetic alterations in DD. The ultimate aim is to unravel which roles the specific genes in the detected sub-networks play in the pathway in the context of the disease and how genetic alterations change these functions in DD. For these more functional experimental, studies are necessary.

13.4 Targeted Sequencing

13.4.1 Ongoing Studies to Identify Genetic Variants in GWAS Loci by Targeted NGS

The SNPs tested in GWAS are selected as a set of informative single SNPs able to tag common haplotype blocks. To explicitly capture causative variants in GWAS-identified DD susceptibility loci, it will be critical to sequence each candidate locus using targeted next-generation sequencing (NGS). By mapping NGS data to the human genome reference sequence, the variability of the entire locus can be exhaustively identified, including both coding and noncoding regions and comprising all common and rare variants (Udler et al. 2010).

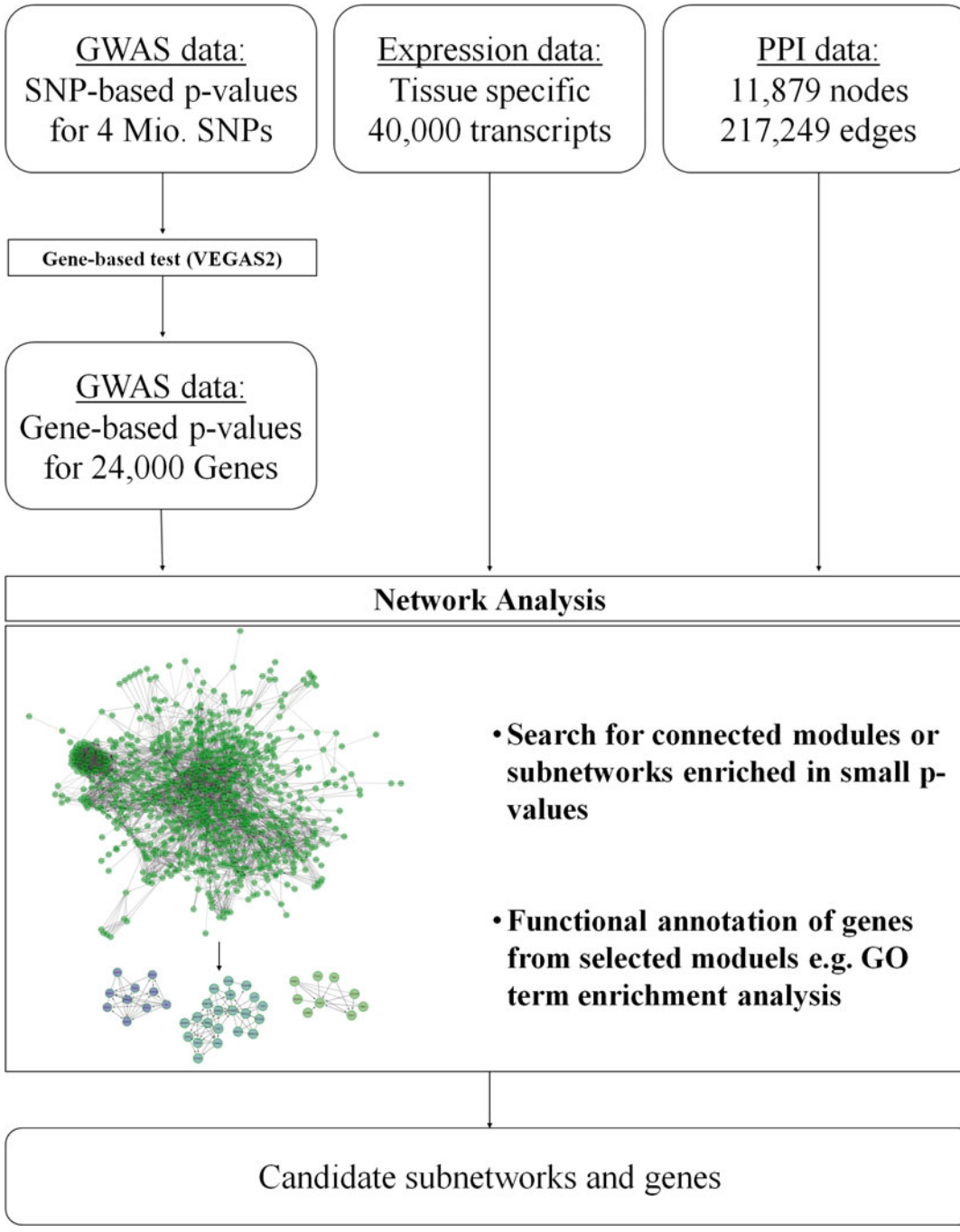

Fig. 13.1 Overview network analysis. Simplified workflow of the network analysis integrating GWAS and transcriptome data to search for disease-specific sub-networks in DD. In the first step SNP-based *p*-values are translated into gene-based *p*-values. Genes with *p*-values are then imposed on protein-protein interaction (*PPI*) data, and a search for connections between genes with small *p*-values is conducted. Once sub-networks (modules) enriched for genes with small *p*-values are identified, these can be validated and further analyzed for functional annotation in the context of the disease. To further increase the power to detect relevant sub-networks, tissue-specific expression data can also be integrated in the network analysis approach

As a first step, we have selected a 500 kb region containing the lead SNP rs16879765 (chromosome 7p14.1) for targeted sequencing (Fig. 13.2). DNA was isolated from peripheral blood of 96 DD patients. The DD-associated locus was enriched in these samples using a custom designed Agilent SureSelect XT2 kit and sequenced on the Illumina HiSeq 2000 platform. Sequencing data are analyzed with the Varbank pipeline (v2.13) (CCG, Cologne) and Ensembl Variant Effect Predictor (http://www.ensembl.org/info/docs/variation/vep/index.html).

Once the potential candidate variants are discovered and validated, the next step will be to prioritize the candidates based on the following criteria: (1) exclude known, assumed harmless variations present in dbSNP databases (http://www.ncbi.nlm.nih.gov/SNP) and published studies; (2) select variants causing changes in protein-coding sequences and likely to compromise protein structure, function, or stability; and (3) select noncoding variants that may affect regulation of gene expression.

13.4.2 Functional Studies of Variants Within Coding Regions

All coding variants identified in DD patients are validated by Sanger sequencing, in particular variants in regions that contain multiple and/or recurrent variants in patients as compared to controls. Then, replication of the results in an independent cohort is needed. The identified variations are analyzed to predict the structure of the gene carrying variations and the function of the resulting protein by using tools such as SIFT (http://sift.jcvi.org/www/SIFT_dbSNP.html), PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2), Mutation Profiling (http://profile.mutdb.org), and ModBase (http://modbase.compbio.ucsf.edu). After identification of a set of DD-predisposing gene variants, in vitro studies to test the functional consequences of these candidates are crucial.

The primary functional studies will focus on the key molecular events in DD development – the aberrant proliferation of fibroblasts and their differentiation into myofibroblasts. After cloning and expression of mutated genes in DD and control cells, cell proliferation is assessed using, for instance, the CyQUANT® Cell Proliferation kits (Thermo), which measures the cellular DNA content. Furthermore, as the expression and organization of α-SMA are hallmarks of myofibroblast differentiation (Tomasek et al. 2002), LightCycler® (Roche) qRT-PCR and Western blotting are employed to detect α-SMA expression. Additionally, myofibroblast contractile activity and migration will be investigated by collagen matrix contraction and in vitro wound healing assays separately.

13.4.3 Functional Studies of Noncoding Regulatory Variants

Many variants associated with GWAS were identified in noncoding regions of the genome, and this has increased the interest in the effect of genetic variants on regulation of gene expression. Recently, expression quantitative trait loci (eQTL) mapping has become a powerful tool to understand how noncoding variants in GWAS loci influence disease risk (Conde et al. 2013; Li et al. 2013). Identification of an eQTL, a genomic locus which regulates transcript expression levels, involves association analysis between genetic markers and gene expression levels typically measured in hundreds of individuals. Microarrays or RNA-seq are often used to measure the expression levels of genes in a genome simultaneously and map these phenotypes to genomic regions represented by genetic markers captured in GWAS. One important advantage of such an approach is that it allows identification of regulators of expression of disease-associated genes if there are variants affecting expression of that regulator (Steiling et al. 2013).

To identify noncoding variants that affect gene expression in DD-associated loci, we use published eQTL and ENCODE data to prioritize genomic variants found by targeted NGS. Using

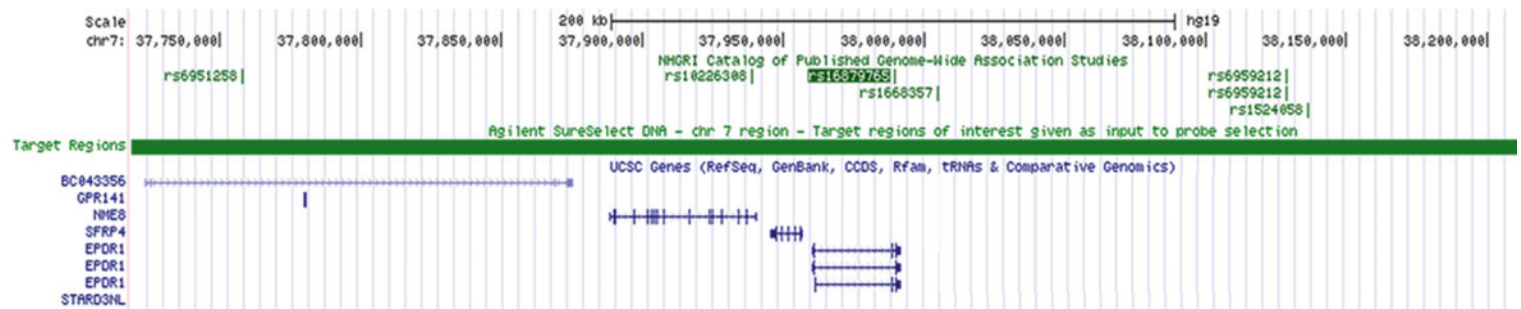

Fig. 13.2 UCSC Genome Browser plot of target region containing rs16879798 for enrichment capturing and sequencing. UCSC Genome Browser plot of target region containing rs16879798 for enrichment captures and sequencing. Target region: chr7:37,714,869 – 38,214,857. Predicted Agilent SureSelect XT2 coverage: 98.3 %

qPCR assays, we test the candidate eQTLs in DD tissues and primary cells derived from DD tissues. A number of bioinformatics tools will then be used to predict possible activities of noncoding variants using, for instance, Genomatix (http://www.genomatix.de), Transfac (http://www.gene-regulation.com/pub/databases.html), and Human Splicing Finder (http://www.umd.be/HSF). Taken together, we expect to identify noncoding variations that underlie inherited differences in expression levels of genes, which is supposed to lead to the identification of genes involved in the susceptibility to DD.

Conclusions

- Dupuytren Disease has a strong genetic basis and unraveling this basis is challenging.
- Network analysis integrating GWAS and differential transcriptome expression data with protein-protein interactions facilitates the identification of modules and pathways perturbed by genetic alterations in DD.
- Targeted sequencing of GWAS loci aims to identify the underling causative genetic variants.
- Most causative genetic variants in DD are expected to lie outside coding regions, and efforts both in computational methods and functional study design must be undertaken to address them.

Acknowledgments and Conflict of Interest Declaration We are particularly grateful to all patients and control persons who participated in the study. The study was approved by the institutional review board and participants provided written informed consent. The project is supported in part by grants from the DFG through the Cologne Cluster of Excellence on Cellular Stress Responses in Aging-Associated Diseases and the Köln Fortune Program of the Faculty of Medicine, University of Cologne. The authors have no conflict of interest to declare.

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Part IV

Collagenase Injection

Marie Badalamente and Steve Coleman,
supported by Paul Werker

Collagenase Injection: Journey from Bench to Current Advanced Clinical Use

14

Lawrence C. Hurst, Marie A. Badalamente, Kerri Kulovitz, and Maria Relevo

Contents

14.1 How It Began

The eponym for Dupuytren Disease was coined because Dupuytren, a French surgeon, performed a surgery using an open transverse incision in 1831 on his coach man patient with a hand contracture. However, Dupuytren Disease was actually originally described earlier in 1614 by Felix Plater of Basel. Some reports describe Dupuytren Disease even earlier in Orkney and Iceland in the twelfth and thirteenth centuries. Interestingly, Englishman John Hunter reported that Dupuytren Disease originated in ligaments and not tendons, in 1777—the year of Dupuytren's birth. Hunter also suggested that surgical fasciotomy might be done to resolve the contractures (Elliot 1989). The introduction of collagenase for the treatment of Dupuytren Disease is a much more recent event. Doctors Hurst and Badalamente invented this therapeutic option for treating Dupuytren Disease with collagenase and have championed its development since the early 1990s (Hurst 2011).

Collagenase was known since the investigations of gas gangrene, by a German scientist E. Maschmann, in 1937 (Maschmann 1937). Ines Mandl, the first woman to earn a PhD from Polytechnic Institute of Brooklyn in 1949, then further studied this enzyme. She isolated and characterized collagenase from *Clostridium histolyticum* in 1953 (Mandl et al. 1953). In 1957 the A.B. Corporation licensed collagenase for burn debridement, and Knoll Pharmaceuticals

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managed the sales for collagenase ointment for burns. A.B. Corporation was located on Long Island and later became BTC (BioSpecifics Technologies Corp).

Dr. Hurst began studying Dupuytren Disease after his hand surgery fellowship with Robert E. Carroll, MD, at New York Orthopedic Hospital at the Columbia Presbyterian Medical Center (1978–1979). Dr. Hurst became Assistant Professor at the State University of New York at Stony Brook. As the first hand surgeon at the new University Hospital at Stony Brook, Dr. Hurst was charged with starting hand teaching, hand research, and the hand surgery clinical service. The Professor and Chair of the Orthopedic Department at the time was Roger Dee, MD., who encouraged Dr. Hurst to focus his research on Dupuytren contracture.

Shortly after Dr. Hurst arrived to Stony Brook, Marie Badalamente, PhD, joined the faculty focusing on cell biology. Together they conducted several studies designed to enhance the basic science understanding of Dupuytren Disease (Hurst et al. 1986; Badalamente et al. 1992, 1996). One study in particular looked at the myofibroblasts, ATPase, and the abnormal collagen of Dupuytren Disease (Badalamente et al. 1983). This was presented at Dr. Robert McFarlane's Canadian Colloquium on Dupuytren Disease on October 9, 1985. It was at the colloquium that Dr. Hurst and Dr. Badalamente met multiple senior Dupuytren Disease investigators including Dr. Graham Stack, Dr. DA McGrouther, Dr. Michael Flynn, Dr. John Hueston, CW Kischer, and several others. In 1987 during Dr. Hurst's Bunnell Traveling Fellowship, he lectured in Oxford on the "Kreb's Cycle" of Dupuytren Disease. This concept was later expanded by Dr. George Murrell (Murrell and Hueston 1990).

In the late 1990s, Drs. Hurst and Badalamente met Dr. Raoul Tubiana and started a collaboration with him and Dr. Caroline Leclercq, which resulted in the textbook "Dupuytren Disease," published in 2000.

Therefore, it was "on the shoulders of giants," like McFarlane, McGrouther, Stack, Tubiana, and many others, that Drs. Hurst and Badalamante continued their study of Dupuytren Disease and developed a nonsurgical treatment option. Their subsequent work on collagenase had a foundation based in basic science and clinical research. The initial work with collagenase started in 1991 and involved the development of a first in category drug as well as a new therapeutic alternative for Dupuytren contracture. In the 1980s, Drs. Hurst and Badalamente were doing research on nerve repair. Tom Wegman, CEO of BioSpecifics Technologies Corporation, approached Drs. Hurst and Badalamente in 1991 about utilizing collagenase to control the amount of fibrosis around microsurgical nerve repairs. It was quickly determined that collagenase would not be helpful in nerve repair but might be very helpful in Dupuytren Disease where removing collagen is the basic goal of treatment.

14.2 A Plan to Study Collagenase for Dupuytren Disease Was Started

It was well known that surgical removal of the collagen "cords" in Dupuytren Disease is an extensive surgical procedure requiring patients to undergo anesthesia in an operating room and also requires a considerable amount of hand therapy postoperatively. There was always the risk of complications, as well as high recurrence rates (Hurst 2011). In addition, patients had to account for a significant loss of time from work, as well as a temporary decrease in the ability to perform their activities of daily living. Surgery was done to improve finger extension but could be complicated by decreased flexion and grip. Drs. Hurst and Badalamente recommended a minimally invasive treatment that could be done with a collagenase injection which would disrupt the collagen cord. It seemed like an excellent concept, especially since collagenase did not cause any immune problems or anaphylactic reactions and had no direct effect on nerves or vessels (Badalamente and Hurst 1996). Furthermore, collagenase manufactured by BTC had been approved for use during burn wound debridement in patients in the USA by the FDA. This prior

human use of collagenase was an important step forward. If a new component (drug) has not been previously approved for human use by the FDA, then three different species toxicology studies have to be done before any human studies to verify its safety. Animal toxicology testing is very expensive. Because collagenase had already been used in human burn wound treatment, further animal toxicology studies were not required by the FDA. Therefore, it seemed like a natural progression to test collagenase in Dupuytren Disease.

The initial investigations of collagenase in the treatment Dupuytren Disease was complicated by the sudden and unexpected appointment of Dr. Hurst as the acting Professor and Chairman of the Orthopedic Department. The early 1990s were a tumultuous time in the Stony Brook Orthopaedic Department's development. Dr. Hurst's research conducted with Dr. Badalamente became just one aspect of a multifaceted job.

To go forth with using collagenase in humans for Dupuytren Disease, an investigational new drug (IND) number was needed from the US Food and Drug Administration. This bureaucratic regulatory process was done by Drs. Hurst and Badalamente, and ultimately an IND was obtained by SUNY Stony Brook from the FDA in 1994. This allowed clinical trials of collagenase with Stony Brook as the sponsor to begin. Orphan Drug Status was also given to Stony Brook by the FDA later in 1997 which provided grants for the research and 7 years of patent exclusivity to the use of collagenase if it could be approved by the FDA and successfully commercialized for Dupuytren Disease.

14.3 Preclinical Lab Work: Systemic Toxicology Studies and Biomechanical Studies

The first investigation involved studying the Dupuytren cords that were removed from patients undergoing surgical fasciectomy. The cords were brought to the lab, injected with various dose units of collagenase, incubated overnight at body temperature, and then pulled to failure (rupture) with a materials testing machine (Starkweather et al. 1996). The results of this study were very promising. It was discovered that the force needed to pull apart the Dupuytren cords was actually less than the force produced during normal finger extension from a closed fist position. This in vitro biomechanical study showed that clostridial collagenase injected into Dupuytren cords obtained from surgical resection could significantly reduce tensile modulus of the cord tissue and allow the cord to break apart easily.

The initial biomechanical testing was expanded by testing more surgical specimens. Early observation using Dupuytren cords treated with 600 units of collagenase revealed a 93 % reduction in tensile modulus compared with control tissue (2.16 Mpa versus 33.02 Mpa). In 3 treated cords, complete disruption of the specimen occurred during tensile testing. In additional studies, 20 Dupuytren cords were surgically removed from patients and randomly assigned to treatment with collagenase (150 units, 300 units, or 600 units) or control buffer. Mechanical testing of tensile modulus was performed 24 h after treatment during which cords were placed under a constant displacement of 9 mm/s until cord rupture (Badalamente and Hurst 1996).

These studies showed a clear inverse relationship between collagenase dose and the force needed to disrupt Dupuytren cords. Comparison of these data with previous reports of the average muscle tendon extensor force of each finger suggested that 300 units collagenase was the minimum effective dose sufficient to cause cord rupture by the normal extensor forces of the index, long, ring, and small fingers. Furthermore, histological examination of collagenase-treated cords revealed collagen lysis, which was increasingly apparent with incremental doses of collagenase (Starkweather et al. 1996; Hurst et al. 1996).

Although these results were promising, the FDA still did not immediately approve the testing of collagenase in humans with Dupuytren Disease. The FDA was concerned collagenase might damage the neurovascular structures in the human palm and fingers. Therefore, an additional study was performed utilizing a rat tail

model. The rat tail has nerves, arteries, veins, small bones, and a tendon. Thus, it was the perfect animal model for a finger. This preclinical in vivo lab safety study showed that collagenase could be safely injected into the tendon of a rat tail without damaging the neurovascular structures, or bones. The injected tendon was disrupted by the collagenase, but the other collagen-containing structures remained intact and the rats' tails remained viable (Badalamente and Hurst 1996).

In this model, the right sacrocaudalis ventralis lateralis (tail) tendon was exposed in adult male rats and injected with purified clostridial collagenase (150 units in 10 μL neutral buffer or 300 units in 10 μL buffer, $n = 7$ per group) or a control solution (10 μL of sterile distilled water; $n = 7$).

Tissue prepared from control animals showed intact collagen bundles and adjacent skin and minimal evidence of collagen microtears. Injection-site sections prepared from animals euthanized at 1 h after injection with 150 units clostridial collagenase revealed minimal collagen lysis within the tendon, with damage evident in some collagen bundles but not in others. In the animals euthanized 24 h after injection of 150 units clostridial collagenase, more extensive collagen lysis was present, with clear evidence of collagen lysis with collagen bundle discontinuity. Similarly, in animals treated with 300 units clostridial collagenase, collagen lysis was evident at both 1 and 24 h following injection, although lysis was considered more extensive at the latter time point. Clearly, collagenase's effect increased during the 24 h time period.

Some tail tendon lysis occurred in all animals receiving 150 or 300 units clostridial collagenase, no extravasation of collagenase to adjacent tissues was noted, and no microhemorrhage other than that associated with the surgical procedure was present. All adjacent structures, including ventral artery and vein, nerve bundles, muscle, and skin, remained intact and showed normal anatomy. In all cases, the sections prepared from tissue proximal and distal to the injection site also showed normal anatomy. After this study was successfully completed, the FDA then approved collagenase for trial experiments in human patients.

14.4 FDA-Regulated Clinical Phase 1 and 2 Trials Begin

The first study done in human patients was done in 1995 and utilized only 1/20 of the dose that is currently used today. So needless to say, none of the patients ($n = 6$) that were treated with this dose experienced any clinical benefit. Clearly, living Dupuytren cords in patient hands were not disrupted by this small injection of collagenase that had disrupted Dupuytren cords in the laboratory studies. Drs. Hurst and Badalamente were disheartened but decided that larger doses should be tried. The FDA then approved a dose escalation study. In this study design, the amount of collagenase given was increased using a dose-doubling scheme. In this type of study, the dose is doubled until a therapeutic effect is achieved or until adverse events suggest toxicity. If therapeutic success cannot be achieved without toxicity, the study has to be discontinued. Ideally, therapeutic success is achieved by doubling the dose before toxicity is encountered. Using this dosing scheme, 1 out of 7 patients experienced a Dupuytren cord rupture, leading Drs. Hurst and Badalamente to believe that collagenase could potentially be used to treat Dupuytren contracture (Badalamente and Hurst 2000).

The next steps were the phase 2 trials followed by two 3 phase trials to examine the efficacy and safety of clostridial collagenase injections with Dupuytren contracture.

The initial *pilot study* using the results of the in vivo biomechanical study as a basis, an open-label, dose escalation, phase 2, pilot study evaluated 35 patients (32 men and 3 women) with a mean age of 65 years. The primary efficacy end point was correction of deformity to within 0–5° of normal (0°) within 30 days of the last injection. The first 6 patients, as previously described, were treated in the dose escalation phase of the protocol and received single injections of 300, 600, 1200, 2400, 4800, or 9600 units of collagenase. No clinical benefit was observed in these

patients. The remaining 29 patients received injections of 10,000 units (0.58 mg) collagenase. Up to 6 repeat injections were given 4–6 weeks apart if the joint angle did not correct to within 0–5° of normal. The mean degree of initial joint contracture was 42° ± 13° for MP joints and 52° ± 16° for PIP joints. Thirty of 34 MP joints (88 %) and 4 of 9 PIP joints (44 %) treated with 10,000 units of collagenase were fully corrected or improved to within 5° of normal. Repeat injections were required in 15 patients. Overall, recurrence occurred in 3 MP joints 2 years post injection and 1 PIP joint 3 months post injection (Badalamente et al. 2002).

Study 101 A single-center, randomized, placebo-controlled, double-blind, phase 2a study was subsequently conducted in 49 patients (42 men and 7 women), 36 patients with MP joint contracture, and 13 patients with PIP joint contracture. The mean age of patients was 65 years. The primary efficacy end point was correction of deformity to within 0–5° of normal extension (0°) within 30 days of the last injection. Patients not meeting the primary end point after one injection in the double-blind study could receive up to 4 additional injections of 10,000 units (0.58 mg) of collagenase on an optional, open-label basis. The open-label extension was available to all patients, including those randomized to receive placebo during the double-blind phase. In the double-blind study, MP and PIP joints were randomized to receive 10,000 units of collagenase ($n = 18$ and $n = 7$, respectively) or placebo ($n = 18$ and $n = 6$, respectively). The mean baseline contracture of joints before collagenase injections was 44° ± 17.4° for MP joints and 53° ± 18.7° for PIP joints. Overall, more joints with cords treated with collagenase than placebo achieved correction of deformity to within 0–5° of normal and within a shorter time. One month after injection with collagenase, 14 of 18 MP joints (78 %) showed correction of contracture to within 0–5° of normal compared to 2 of 18 MP joints (11 %) after injection with placebo. The 4 patients who did not achieve correction of deformity to within 0–5° of normal with the first injection were treated again, and all showed correction of contracture to within 0–5° of normal 1 month after the second injection. Of the patients with PIP joint contractures, 5 out of 7 (71 %) treated with collagenase and none treated with placebo were corrected to 0–5° of normal 1 month post injection. Flexion and grip strength did not significantly change compared with baseline values in either the MP- or PIP-treated or placebo groups. Recurrence occurred in 4 MP joints and 4 PIP joints in mean follow-up periods of 4 years and 3.8 years, respectively. Further follow-up at 5 years showed recurrence in only one additional MP joint (Badalamente et al. 2002).

Then in 2001 the FDA intervened again and proposed the question "are you using the minimal effective dose to achieve the desired outcome?" To answer this question, an additional, multicenter phase 2 study was designed, in cooperation with our colleague Dr. VR Hentz at Stanford University. Eighty patients (64 men and 16 women) with a mean age of 63.9 years took part in a randomized, double-blind, placebo-controlled, dose-response, phase 2b trial conducted at 2 test centers. The objective was to determine again if, indeed, 10,000 units (0.58 mg) was the minimum safe and effective dose. Fifty-five patients had MP joint contractures (mean baseline contracture of 50° ± 4.9°) and 25 had PIP joint contractures (mean initial contracture of 49° ± 9.8°). Joints were randomized to receive a single injection of 2500 (0.145 mg), 5000 (0.29 mg), or 10,000 (0.58 mg) units collagenase or placebo.

A comparison of dose groups showed that in both MP and PIP joints, the return to normal extension (0–5°) was higher in patients who received 10,000 units of collagenase 1 month after injection compared with the lower collagenase doses or placebo. Eighteen of 23 patients (78 %) who received 10,000 units of collagenase responded to normal extension by 1 month compared to 10 of 22 patients (45 %) who received 5000 units and 9 of 18 (50 %) of patients who received 2500 units. No response was observed in the placebo group. An open-label extension of this study permitted up to 4 additional 10,000-unit collagenase injections. Overall, 59 % (22 out

of 37) achieved 0–5° with retreatment; success was higher in MP joints (66.6%) than PIP joints (46.2%). Recurrence occurred in 1 MP joint and 1 PIP joint after mean follow-up periods of 2 years and 12.5 months, respectively. Further follow-up at 5 years indicated recurrences in 5 (of 37) MP joints and 4 (of 20) PIP joints.

Safety in Phase 2 Studies In all 3 phase 2 studies, collagenase injections were well tolerated. Some minor, transient adverse events, such as injection site tenderness, hand ecchymosis, and edema, were reported, but all resolved within 6–7 weeks (mean time to resolution of 1–2 weeks) of the injection. Collagenase injection did not induce an adverse systemic immune reaction, even after repeated administration. Although some patients had detectable serum IgE titers following collagenase injection, no induced allergic reactions were reported (Badalamente and Hurst 2007).

Summary of Phase 2 Studies Data from the phase 2 studies showed that clostridial collagenase injection provides superior clinical success rates compared with placebo injections and has merit as a nonsurgical treatment for patients with Dupuytren contracture. After these studies were performed, the FDA team overseeing the clinical trials then changed. This new team had approved Vioxx which was later taken off the market. Needless to say, this team was very cautious about approving any other drugs, including collagenase.

14.5 Commercialization and Manufacturing Woes

Next, the issues related to commercialization and manufacturing threatened to derail the development of collagenase for Dupuytren contracture treatment. Phase 3 trials can be extremely expensive, and, therefore, BTC sold their licensing technology to Auxilium Pharmaceuticals, and the IND, which was held by the University at Stony Brook, was transferred to Auxilium in 2005. Pfizer also got permission to market collagenase in Europe as Xiapex in 2008. A revised US Patent was then reissued and granted in 2007 to BTC.

It was at this point that Dr. Hurst and Dr. Badalamente thought everything was going well and collagenase would finally be fully approved after phase 3 trials. However, the FDA also looks at manufacturing of each new drug. Since BTC was manufacturing collagenase in a small factory in Puerto Rico, the FDA said it was out of date because it was over 30 years old. The FDA would not approve any drugs manufactured from this old factory and required that a new manufacturing facility be built. Thus, the next challenge was to build a new factory. Fortunately, Auxilium was able to build the new factory and finally started to produce the drug. Finally, collagenase acceptable to the FDA was available and Phase 3 trials could begin.

14.6 FDA-Regulated Clinical Phase 3 Trials Begin

Study 303 Based on the promising data from phase 2 investigations, the efficacy and safety of clostridial collagenase were assessed in a phase 3 randomized, double-blind, placebo-controlled clinical trial at Stony Brook Medical Center. This trial included 35 patients with Dupuytren contracture who were randomized in a 2:1 ratio to receive injections of collagenase ($n=23$; 10,000 units (0.58 mg) or placebo ($n=12$). In total, 21 patients had affected MP joints, and 14 had affected PIP joints: mean baseline joint contracture was 51° for MP joints and 46° for PIP joints. Primary and, when possible, secondary and tertiary joints were identified for each patient, resulting in a total of 55 affected joints. Patients could receive up to 3 injections in the primary joint at 4- to 6-week intervals. Those who achieved correction to 0–5° of normal after the first injection were eligible to be re-randomized to further treatment for a secondary or tertiary joint. All patients wore splints at night for 4 months after injection. The primary efficacy end point was a reduction in deformity in the primary joint to within 0–5° 30 days after the last injection. Additional end points included time to clini-

cal success, number of injections required to achieve correction to 0–5° of normal, and recurrence (defined return of contracture to ≥20° in successfully treated joints).

Of the 35 randomized patients, 33 completed the double-blind study. In addition, 9 patients were re-randomized after successful treatment of the primary joint: 6 received collagenase and 3 received placebo. One tertiary joint was also treated with collagenase. Overall, 21 of 23 (91 %) patients who received collagenase and 0 of 12 (0 %) who received placebo for a primary joint achieved 0–5° of normal ($P < .001$). Both joint types responded well to collagenase treatment with correction to 0–5° of normal attained in 12 of 14 (86 %) MP joints and 9 of 9 (100 %) PIP joints. Furthermore, 16 of 23 patients achieved correction to 0–5° of normal with a single collagenase injection, whereas 2 patients required 2 injections and 3 patients required 3 injections. Overall, the mean number of injections for correction to 0–5° of normal was 1.4, and median time to clinical success was 8 days. Correction to 0–5° of normal was also achieved in 5 of 6 (83 %) collagenase-treated secondary joints and in the only collagenase-treated tertiary joint.

Study 404 Patients in the double-blind study 303 who failed to achieve correction to 0–5° of normal, or who had other involved joints of the same or contralateral hand, were eligible to continue treatment in the open-label extension study (study 404). During this study, patients could receive up to 3 injections of collagenase (10,000 units) in a single joint, with no more than a total of 5 injections across both double-blind and open-label studies. Nineteen patients with 35 involved joints were included in the open-label study, including 15 patients who received placebo to either primary or secondary joints in the double-blind phase and 4 patients who failed to achieve clinical success while receiving collagenase during the double-blind study. Clinical end points in the open-label study were the same as those used in the double-blind study. In total, 17 (89.5 %) of 19 patients achieved correction to 0–5° of normal in at least 1 treated joint. Similar rates of correction to 0–5° of normal were achieved in MP and PIP joints. In total 27 of 35 (77 %) affected joints were successfully treated, including 14 of 16 (88 %) MP joints and 13 of 19 (68 %) PIP joints. Importantly, 23 affected joints were successfully treated with a single injection, with response rates similar in MP and PIP joints. The mean number injections required to achieve correction to 0–5° of normal was 1.5 for MP joints and 1.3 for PIP joints. In total, throughout the double-blind and open-label studies, a total of 62 affected joints were treated, of which correction to 0–5° of normal was achieved in 54 (87 %). All patients were subsequently followed for 12 months, and 27 of 54 joints were followed for 2 years. During this period, 4 PIP joints and 1 MP joint showed recurrence of contracture. For the PIP joints, recurrence was 20° and 30° at 12 months and 40° at 24 months.

14.6.1 Safety/Adverse Events

In general, collagenase therapy was well tolerated in phase 2 and phase 3 clinical studies, with all adverse events graded as mild to moderate and most resolving within about 1–3 weeks. Injection-site pain, hand ecchymosis, and edema occurred but resolved with mean times to resolution of 1–2 weeks. Lymphadenopathy (usually axillary or elbow) was also observed in a minority of patients (approximately one third) in both phase 2 and phase 3 studies.

There were 11 skin lacerations at cord rupture in the phase 3 studies. These lacerations occurred primarily in patients who had experienced severe baseline (>80°) contracture over many years. All lacerations were effectively healed through secondary intent without surgery and did not affect clinical outcome. Finally, no systemic immunological adverse events were reported.

Next, Auxilium sponsored and started the CORD (Collagenase Option for Reduction of Dupuytren) studies. This was a massive undertaking with 16 sites in the USA participating as well as 5 sites in Australia. This phase 3 trial would be a final data source for the new drug application that would be submitted to the FDA

for collagenase treatment of Dupuytren Disease. However, just before this study was about to begin, it was noticed that some of the bottles containing the lyophilized collagenase (Xiaflex) did not have the usual size "cake" of lyophilized drug. Some of the cakes were smaller than usual, and the bottles had a milky-looking stain on the inside of the glass bottle containing the drug. Although the medication still worked, it didn't look right. The FDA immediately put the final phase 3 trial on hold. It took nine months to sort out that a little moisture was leaking into the bottles during manufacturing, and some of the collagenase protein was partially dissolved and caused this milk glass appearance instead of the normal full-sized "cake" appearance. Once the moisture leakage was identified, new tighter rubber caps were designed for the bottles containing the lyophilized Xiaflex, and the "cake" all remained intact. Once the FDA approved this manufacturing change, the CORD studies were started. The study showed that 64 % of the MP joints were able to be fully extended after treatment.

CORD I and CORD II In these studies (Hurst et al. 2009), patients were required to have a minimum 20° of contracture and were randomized using a ratio of 2:1 to receive collagenase (0.58 mg) or placebo. The primary objective of CORD 1 and CORD 2 is normalization of the joint to within 0–5° of normal (0°) after up to 3 injections of study treatment. Upon completion of a double-blind phase, patients who initially received placebo or who have other affected joints were eligible for enrollment in open-label extension phases, during which, all patients will receive collagenase treatment.

Importantly, a statistically significant difference was observed in the ability of clostridial collagenase to meet the primary endpoint—correction to 0° to 5° of normal after the last injection—compared with placebo. Overall, 64 % of joints treated with collagenase vs. 6.8 % treated with placebo ($P < .001$) were corrected to 0–5° of normal after the last injection in CORD I. In CORD 2, the rates were 44.4 % vs. 4.8 % ($P < .001$). The most common adverse events reported in CORD I and II were pain, swelling, bruising, and pruritus at the injection site. No systemic allergic reactions were reported. Overall, 7 serious adverse events possibly related to collagenase were reported, including 2 confirmed tendon ruptures, 1 pulley ligament injury, and 1 complex regional pain syndrome.

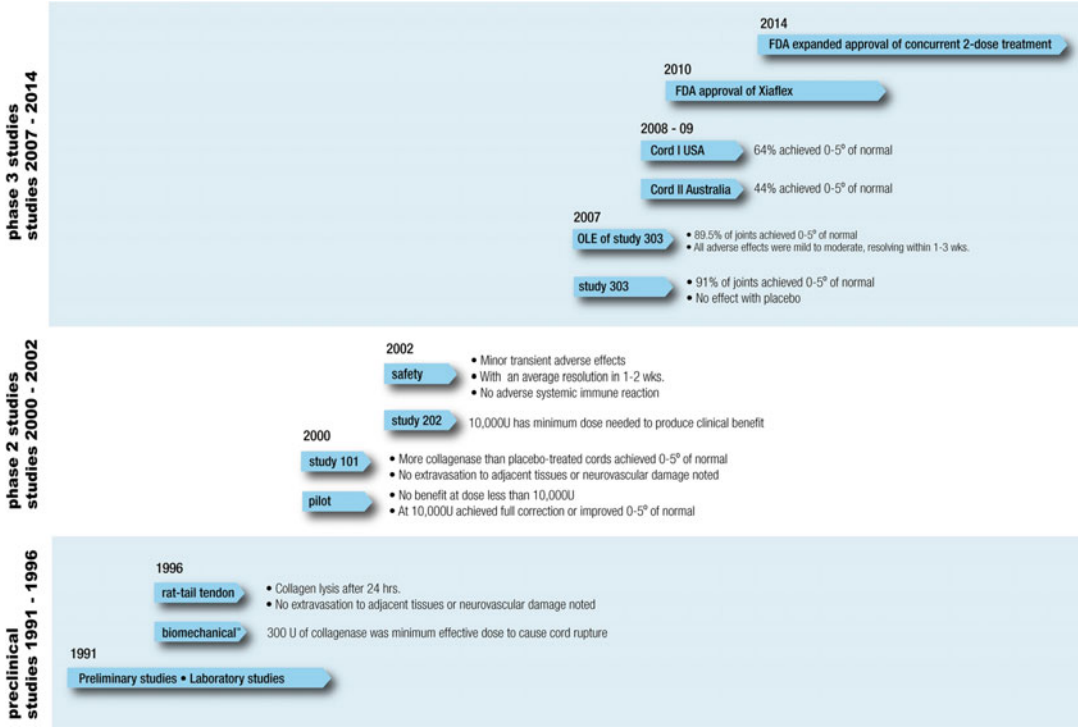
The CORD study was published in *The New England Journal of Medicine* in 2009, *Injectable Collagenase Clostridium Histolyticum for Dupuytren Contracture* (Hurst et al. 2009).

In September of 2009, the FDA convened an Advisory Committee to look at all the data from all collagenase studies and the Advisory Committee stated that they would recommend that Xiaflex be approved for use in humans. The committee vote was 12-0 in favor of approval. Finally, in February of 2010, the US FDA approved Xiaflex. In 2010, there were only six biologic compounds to be approved by the FDA to become drugs. Dr. Hurst, Dr. Badalamente, and Dr. Wang (for a separate adhesive capsulitis study) were given the honor of the Orthopaedic Research and Education Foundation and American Academy of Orthopaedic Surgeons Clinical Research Award. There is only one of these awards given per year in the USA. A symposium was then held in April of 2010 in Stony Brook focused on Dupuytren Disease and treatment with Xiaflex. A DVD of this symposium was donated to the American Society for Surgery of the Hand for distribution as an educational resource (Hurst and Badalamente 2010).

14.7 Summary of Studies in Dupuytren Contracture (Table 14.1)

Injectable clostridial collagenase is a promising treatment for patients with Dupuytren contracture. Dose-ranging, phase 2 clinical trials identified an optimal collagenase dose of 10,000 units (0.58 mg), balancing excellent clinical efficacy outcomes with a favorable tolerability profile. High rates of correction of joint contracture to 0–5° of normal after the last injection were

Table 14.1 Timeline for the development of injectable collagenase *Clostridium histolyticum* for the treatment of Dupuytren Disease



attained in both MP and PIP joints and in patients of all ages, as demonstrated in the phase 3 studies. Encouragingly, clinical efficacy appears to be reasonable with long-term follow-up of patients from the first phase 3 clinical trial. Adverse events are typically local reactions to the injection, are mild to moderate in severity, and dissipate within 1–3 weeks of injection. No serious or systemic immunological adverse events have occurred.

14.8 Insurance Approval

In February 2010, Xiaflex was approved by the FDA; however, insurance companies in the USA still considered it experimental and were not routinely covering the treatment of Dupuytren contracture with Xiaflex. Finally, in the summer and fall of 2010, medical insurance coverage for Xiaflex became available for most patients. Once this payment bearer was overcome, there were 852 patients on the waiting list at the University Hand Center at Stony Brook who were requesting treatment for their Dupuytren contractures with Xiaflex. It took two years to treat the backlog of 852 patients.

In January 2011 the public media became involved in the Dupuytren Disease and the Xiaflex story. Xiaflex was used in the TV show "Royal Pains," where a concierge physician in the episode called "Muligan" injected a Xiaflex to his friend's hands over lunch and manipulated his fingers during the golf outing the next day. Obviously this was a TV dramatization which took considerable literary license with the FDA's labeling recommendations. However, this single TV show did increase the US public's awareness of Dupuytren Disease and Xiaflex treatment.

After Xiaflex became available for clinical use in the USA, other international pharmaceutical companies made partnership arrangements with Auxilium. These included Pfizer in 2008 and SOBI in 2014 to provide Xiapex (Xiaflex's European

name) in the European Union, Actelion provided it in Canada and Australia in 2011, Asahi Kasei Pharmaceutical Corporation in Japan in 2012 with release in 2016, and lastly Auxilium which was bought by Endo Pharmaceuticals in 2015.

Xiaflex (Xiapex in Europe) is recommended for patients with a palpable cord causing MP joint contractures of 20–30° or more as well as PIP joint contractures of 20° or more that are getting progressively worse over time and a positive tabletop test. For the actual injection of Xiaflex, Dr. Hurst prefers to use a 1 mL hubless syringe with a fixed 27 gauge needle. 0.25 mL is injected for the MP joint and 0.20 mL for the PIP joint; each injection contains 0.58 mg of collagenase (Xiaflex). Aliquots of the 0.58 mg dose are placed in 3–5 separate locations in the Dupuytren cord. For the manipulations, approximately 9 cc of 1 % lidocaine is used with 1 cc of bicarbonate buffer to give a per manipulation local field block. The finger manipulation or finger extension procedure is always done in a four-step manner: (1) extend the MP joint with PIP flexed, (2) extend the PIP joint with the MP flexed, (3) extend the MP and PIP joints simultaneously, and (4) with the MP and PIP extended, push on any areas with residual cord with the surgeon's opposite thumb or index finger. During the manipulation, it is important to be as gentle as possible to avoid skin tears. Skin tears often start through areas of skin with blood blisters so extra caution is warranted when blisters are present after injection.

14.9 The Future of Xiaflex in Dupuytren Disease

The use of Xiaflex is currently approved for use in MP and PIP joints; however, Dr. Hurst has successfully used it in DIP joints and thumb contractures and first web contractures as well. Although these treatments are "off-label" uses of Xiaflex, Xiaflex has proved to be beneficial in Dr. Hurst's patients for DIP flexion contractures, web contractures, and thumb contractures. Xiaflex has also been used successfully in the treatment of cord combinations such as the "Y" cord which is a combination of a central cord and a natatory cord. By dividing a single Xiaflex dose and by using two concurrent doses in the same hand, which has now been FDA approved, multiple complex cord combinations can now be treated in a single sitting. Recent studies have also allowed the FDA labeling to include delayed finger extension timings at 48 and 72 h after injection. Concurrent double-dose treatment has proven to be both efficacious and safe to administer for contractures of two joints in the same finger or for fixed MP or PIP flexion contractures in different fingers in the same hand (Gaston et al. 2015).

A study was performed where patients with 2 or more 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 1 or 2 cords in the same hand (1 injection per affected joint) during the same visit (Gaston et al. 2015). Finger extension was performed approximately 24, 48, or 72 or more hours later. Changes in FFC (fixed flexion contracture) and range of motion, incidence of clinical success (FFC $\leq 5°$), and adverse events (AEs) were summarized. The study enrolled 715 patients (725 treated joint pairs), and 714 patients (724 joint pairs) were analyzed for efficacy. At day 31, mean total FFC (sum of 2 treated joints) decreased 74 %, from 98° to 27°. Mean total range of motion increased from 90° to 156°. The incidence of clinical success was 65 % in metacarpophalangeal joints and 29 % in proximal interphalangeal joints. Most treatment-related AEs were mild to moderate, resolving without intervention; the most common were swelling of treated extremity, contusion, and pain in extremity. The incidence of skin lacerations was 22 % (160 of 715). Efficacy and safety were similar regardless of time to finger extension.

Therefore, collagenase *Clostridium histolyticum* (Xiaflex) can be used to effectively treat 2 affected joints concurrently without a greater risk of AEs than treatment of a single joint, with the exception of a small increased skin tear rate. The incidence of clinical success in this study after 1 injection per joint was comparable to phase 3 study results after 3 or more injections per joint. There is no greater risk of adverse events than treatment of a single joint, with the exception of

skin laceration. Two concurrent CCH injections may allow more rapid overall treatment of multiple affected joints, and the ability to vary the time between CCH injection and the manipulation may allow physicians and patients' greater flexibility with scheduling treatment. Manipulations have been performed successfully up to 48 and 96 h after injection of Xiaflex.

In conclusion, Xiaflex/Xiapex is an excellent and useful alternative to surgery for patients with advanced Dupuytren Disease. However, whether a Xiaflex injection or surgery is performed, the Dupuytren cord can still recur. The success in treating patients with Dupuytren contracture comes from experience in making a decision with your patient as to the best treatment option for the best outcome possible. The surgeon and patient must always understand that Dupuytren Disease cannot truly be cured but only managed and that recurrence is always a possibility.

Conflict of Interest Statement Lawrence C. Hurst and Marie Badalamente of Partial Xiaflex/Xiapex royalty from BioSpecifics Technologies Corp. Marie Relevo and Kerri Kulovitz have nothing to declare.

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15 Efficacy of Using Local Anesthesia Before Collagenase Injection in Reducing Overall Pain Experience in Patients Treated for Dupuytren Contracture: A Quasi-Randomized Study

Jesper Nordenskjöld, Eva Ahlgren, Johanna Waldau, Markus Waldén, and Isam Atroshi

Contents

15.1 Hypothesis

Collagenase injection is increasingly used as a nonsurgical treatment for patients with Dupuytren contracture (Atroshi et al. 2014). In the clinical trial by Hurst et al. (2009) collagenase was injected into the cords without prior local anesthesia to avoid a potential confounding factor. In our clinical practice, 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.

15.2 Methods

Consecutive patients with Dupuytren contracture scheduled for collagenase injection were assigned to one of two groups (by alternating scheduled clinics): one received local anesthesia, as a nerve block in the proximal palm, approximately 20 min before collagenase injection (LA group), and the other received the collagenase injection without anesthesia (no-LA group). The eligibility criteria for treatment were a total extension deficit

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of >20° in the metacarpophalangeal joint and/or proximal interphalangeal joint in at least one finger and the presence of a palpable cord. An off-label modification of the standard collagenase injection technique was used (Atroshi et al. 2015). 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, in accordance with the guidelines established by the Department of Anesthesia, Skåne University Hospital (the amount of added bicarbonate is higher than that commonly advocated in the literature). 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. Previous studies assessing acute pain with the VAS scale have concluded that a difference of 1.3 is clinically significant (Gallagher et al. 2001). To be able to show a difference of this magnitude, we calculated a sample size of at least 50 patients per group (90 % power, 5 % significance, SD 2.0).

15.3 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 (Fig. 15.1); 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

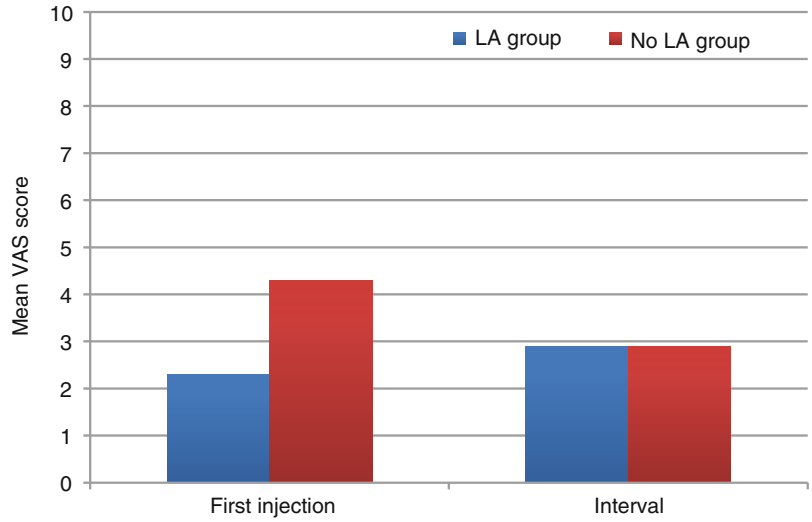

Fig. 15.1 Experienced pain during injection and interval. Mean visual analog scale (*VAS*) scores for pain experienced during the first injection (buffered mepivacaine in the local anesthesia [*LA*] group; collagenase in the no-LA group) and during the time period (1 or 2 days) from the injection to the finger extension procedure

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 ($p = 0.9$). No adverse events related to the local anesthesia occurred.

15.4 Summary

In patients with Dupuytren contracture treated with collagenase injection, administering local anesthesia before the collagenase injection significantly reduces the patients' pain experience at the time of injection. It does not however reduce the pain experienced during the time interval up to the finger extension procedure because the effect of mepivacaine has a relatively short duration that is not prolonged by the sodium bicarbonate.

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16 Effect of Delayed Finger Extension on the Efficacy and Safety of Collagenase Clostridium Histolyticum Treatment for Dupuytren Contracture

Gary M. Pess

Contents

16.1 Introduction

Dupuytren Disease is a benign fibromatosis of the fascia of the hand and fingers. It begins with a palpable mass or nodule. This is usually located between the proximal palmar crease and distal palmar crease, but the nodule may first present in the finger. Enlargement of the nodule leads to the development of pathologic cords which thicken and contract, causing contracture of the metacarpophalangeal (MP) and proximal interphalangeal (PIP) joints. It is very common for patients to have multiple joints and fingers affected (Dahlin et al. 2013).

Collagenase clostridium histolyticum (CCH; brand names Xiaflex and Xiapex) is an approved nonsurgical treatment for adults with Dupuytren contracture and a palpable cord. CCH is injected into the collagen cord causing contracture of the affected joint. This is followed by a finger extension procedure, which helps to disrupt the cord (Hurst et al 2009). CCH injection can be repeated at 4-week intervals with a maximum of three injections per joint.

The US Food and Drug Administration (FDA) labeling of CCH restricted use of CCH to treat only one affected joint at a time with the finger extension procedure performed 24 h after injection. However, in clinical practice, this restriction to 24 h may not be practical for physicians or convenient for patients. Safe delay of the finger extension procedure to 48 h and 1 week post-injection (Manning et al. 2013; Mickelson et al. 2014) has been reported. The effects of varying the time to finger extension procedure on safety and efficacy was evaluated as a secondary objective of a study in which subjects received concurrent administration of two CCH injections into cords in the same hand to treat two joints with Dupuytren contracture with palpable cords (Gaston et al. 2015); Coleman et al. 2014).

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16.2 Materials and Methods

Adult subjects with ≥2 contractures in the same hand caused by palpable cords participated in a 60-day, multicenter, open-label phase 3b study. Two CCH doses (each 0.58 mg) were injected into a cord or cords in the same hand (one injection per affected joint) during the same visit. A finger extension procedure was performed approximately 24, 48, or 72 h after CCH administration. Local anesthesia with lidocaine was allowed. To attain collection of sufficient data for each finger extension time point, investigators were asked to distribute subjects among the three different finger extension times.

Patients were excluded if they had previous surgery on the joints to be treated within 6 months before CCH injection, received any collagenase treatments within 30 days, received anticoagulant medication (except aspirin ≤150 mg/day) within 7 days, had a known allergy to collagenase, and were pregnant or breastfeeding.

Final data included 714 patients, with 724 joint pairs analyzed for efficacy. The joints to be treated were selected at the screening visit. All subjects had two different affected joints treated on the same hand. On day 1, goniometry measurements were performed prior to treatment. Two full 0.58-mg CCH doses were injected into 1 or 2 cords in the same hand. There was one injection per joint. A finger extension procedure was performed approximately 24, 48, or 72 h after CCH administration. Local anesthesia was allowed.

Joint contracture was measured using finger goniometry on days 15 and 31. Range of motion (ROM) was calculated as the difference between full finger flexion and full finger extension. Efficacy variables measured were percent change of FFC and ROM from baseline at day 31 and clinical success (FFC ≤5° at day 31).

Adverse events (AEs) were recorded throughout the study period. AE severity was characterized as mild (transient, easily tolerated by the patient), moderate (caused discomfort and interrupted usual activities), or severe (caused considerable interference with usual activities and may have been incapacitating or life threatening).

Changes in total FFC and total ROM were summarized by time of finger extension (24, 48, or ≥72 h). Changes in FFC and ROM in individual joints were summarized by joint type (MP, PIP) for joints at each finger extension time. Rates of clinical success were summarized by joint type and finger extension time. Adverse events were summarized by finger extension time.

16.3 Results

Improvement in FFC at day 31 was similar regardless of the time to finger extension procedure. For total FFC (joint pairs), mean % reduction in FFC was 75 %, 75 %, and 73 % for finger extension at 24, 48, and ≥72 h, respectively. For MP joints, mean % reduction in FFC was 84 %, 81 %, and 84 % for finger extension at 24, 48, and ≥72 h, respectively. For PIP joints, mean % reduction in FFC was 64 %, 66 %, and 60 % for finger extension at 24, 48, and ≥72 h, respectively.

Improvement in ROM at day 31 was similar regardless of the time to finger extension procedure. For total FFC (joint pairs), mean increase in ROM was 67°, 68°, and 64° for finger extension at 24, 48, and ≥72 h, respectively. For MP joints, mean increase in ROM was 36°, 36°, and 34° for finger extension at 24, 48, and ≥72 h, respectively. For PIP joints, mean increase in ROM was 29°, 30°, and 29°for finger extension at 24, 48, and ≥72 h, respectively.

Clinical success was achieved for 65 % of MP joints and in 29 % of PIP joints following a single injection per joint. Time of finger extension after injection had no impact on the rate of clinical success for either MP or PIP joints (Table 16.1).

Treatment-related AEs (Table 16.2) were common, but most were mild (42 %) or moderate (48 %) in severity. There was no difference in the incidence of treatment-related AEs between the three finger extension groups. The rate of lacerations was 22 % (160/715) but appeared lower when finger extension was performed at 72 h than at 24 or 48 h

Sixteen patients reported 1 or more treatment-emergent SAE (severe adverse effect); 6 patients had SAEs that were considered treatment related or possibly treatment related: 1 with anaphylactic reaction (0.1 %), 1 with tendon rupture (0.1 %), 1 with hemorrhage (0.1 %), 1 with lymphangitis (0.1 %), 1 with deep vein thrombosis and pulmonary embolism (0.1 %), and 1 with lymphadenopathy, malaise, edema peripheral, and pain in the extremity (0.1 %).

Table 16.1 Rate of clinical success in MP and PIP joints following a single injection per affected joint, by time to finger extension

	MP joints	Clinical success	PIP joints	Clinical success
	N	*n* (%)	*N*	*n* (%)
24 h after CCH injection	325	213 (66)	211	62 (29)
48 h after CCH injection	377	237 (63)	219	70 (32)
≥72 h after CCH injection	194	129 (65)	122	26 (21)

Clinical success defined as FFC ≤5° within 30 days after CCH injection
CCH collagenase clostridium histolyticum, *MP* metacarpophalangeal, *PIP* proximal interphalangeal

16.4 Discussion

CCH has been providing an alternative to surgery for patients with Dupuytren contracture since the FDA approved its use in 2010. Efficacy and safety have been demonstrated in a 5-year follow-up study (Peimer et al. 2015) and in numerous clinical trials (Hurst et al. 2009; Gilpin et al. 2010; Witthaut et al. 2013). The previous studies all utilized an identical protocol following the procedure established in the CORD I and CORD II studies. Common issues that arise in clinical practice were not considered, such as treating more than 1 joint at the same time and performing the finger extension procedure later than 24 h post-injection.

Compared with the reported results of the phase 3 studies, this study using a single injection in each of 2 affected joints, administered at the same time, showed comparable efficacy. Clinical success, FFC ≤5° within 30 days after a single CCH injection, was achieved in 65 % of MP joints and 29 % of PIP joints.

Table 16.2 Most common treatment-related adverse events (TRAE)

Adverse event, *n* (%)	Safety population (*n* = 715 patients)	24 h (*n* = 268 joint pairs)	48 h (*n* = 299 joint pairs)	≥72 h (*n* = 158 joint pairs)
≥1 TRAE	680 (95)	251 (94)	292 (98)	147 (93)
Peripheral edema	552 (77)	188 (70)	255 (85)	117 (74)
Contusion	419 (59)	125 (47)	194 (65)	108 (68)
Pain in extremity	361 (50)	119 (44)	171 (57)	76 (48)
Laceration	160 (22)	65 (24)	68 (23)	27 (17)
Pruritus	106 (15)	39 (15)	61 (20)	8 (5)
Injection site pain	101 (14)	49 (18)	41 (14)	11 (7)
Lymphadenopathy	93 (13)	33 (12)	46 (15)	17 (11)
Blood blister	89 (12)	36 (13)	42 (14)	11 (7)
Injection site hematoma	59 (8)	19 (7)	23 (8)	17 (11)
Axillary pain	51 (7)	21 (8)	23 (8)	8 (5)
Injection site hemorrhage	45 (6)	29 (11)	16 (5)	0
Injection site swelling	42 (6)	14 (5)	15 (5)	13 (8)
Ecchymosis	37 (5)	14 (5)	15 (5)	8 (5)

Incidence ≥5 % of patients
TRAE treatment-related adverse event

Two concurrent injections of CCH were well tolerated in this study. AEs was similar to those reported in phase 3 studies, except for skin lacerations, which were more frequent in this study (22 %). This increase in lacerations may be due to the administration of 2 CCH injections. Other factors include the use of anesthesia prior to the finger manipulation procedure allowing for greater force to be applied, increased investigator experience with the manipulation procedure, and diminished fear of causing skin lacerations since investigators had previously witnessed the rapid healing of skin lacerations with only local wound care. There was no increased risk of tendon rupture after two concurrent injections of CCH compared with multiple single injections.

There was no effect on efficacy or overall safety by varying the timing of the finger extension procedure after injection. Improvements in FFC and ROM as well as rates of clinical success were comparable for joints that had finger extension performed at approximately 24, 48, or 72 h. The rate of skin laceration was lower when finger extension was performed at 72 h (17 %) than at 24 or 48 h (23–24 %). Allowing the finger extension procedure to be performed after 24 h, without a change in efficacy or safety, allows for greater flexibility for both patients and their treating physicians (Gaston et al. 2015).

16.5 Case Example

Patient is a 60-year-old male with an 11-year history of bilateral Dupuytren Disease. He denies any family history. Prior treatment included percutaneous needle fasciotomy right little finger (Feb 2007), partial palmar fasciectomy right little finger (Nov 2007), partial palmar fasciectomy left ring and little fingers (May 2009), and percutaneous needle fasciotomy right thumb and little finger (Feb 2012).

He complains of increased difficulty with shaking hands and grabbing around large objects. Patient chooses to have two simultaneous injections of CCH with a delayed finger extension procedure. Figure 16.1a–g show the hand before and after treatment.

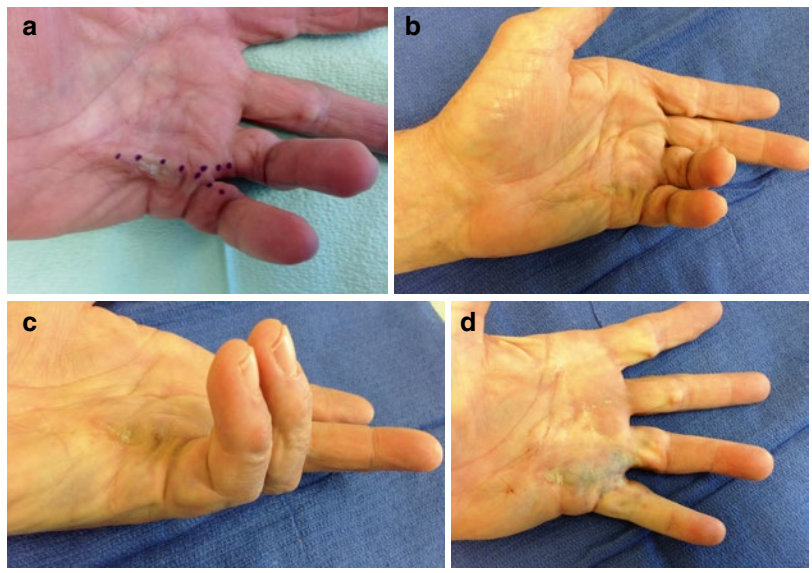
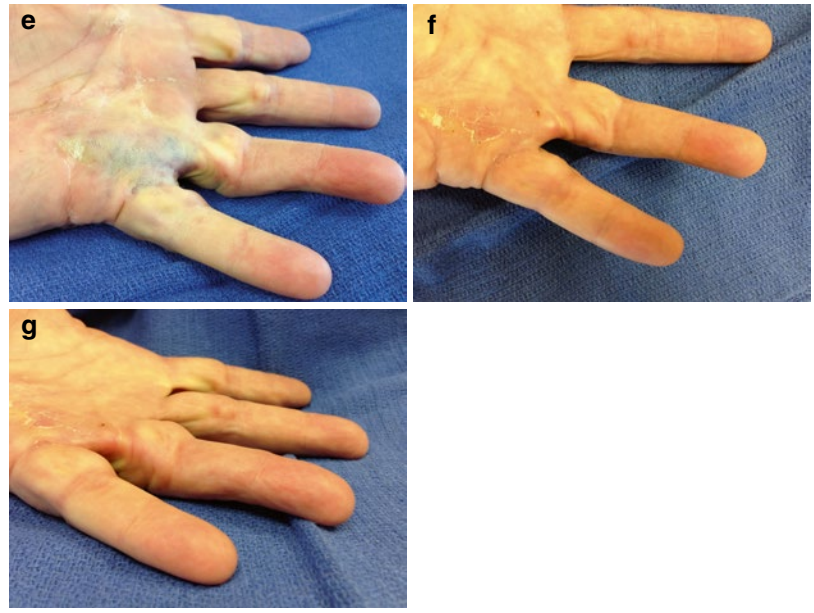


Fig. 16.1 The hand before and after treatment. (**a**) Prior to injection of CCH: Dupuytren contracture left ring finger MP 27° and PIP 75°; left little finger MP 39° and PIP 56°. Post-injection of CCH: there was no spontaneous correction. Contusion and peripheral edema are noted (**b**, **c**). Finger extension procedure performed at 72 h post-injection of CCH: there was correction of contracture left ring finger MP 0° and PIP 5°; left little finger MP 0° and PIP 0° (**d**, **e**). Follow-up at 31 days: excellent maintenance of correction (**f**, **g**)

Fig. 16.1 (continued)



Conclusion

Concurrent injections of CCH to treat two Dupuytren contractures in 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 influence the clinical response in terms of efficacy or safety. The ability to vary the time between CCH injection and the finger extension procedure allows for greater flexibility for both physicians and patients.

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The Use of Dynamic Dorsal Splint for Dupuytren Rehabilitation After Collagenase Injection

17

Massimo Corain, Roberta Sartore, and Roberto Adani

Contents

17.1 Introduction

Dupuytren Disease (DD) is still a challenge for the hand surgeon. There are different surgical and conservative techniques available (Dias et al. 2013; Henry 2014; Murphy et al. 2014). They are all options, but none of them represents the definitive treatment.

In 2010, the US Food and Drug Administration allowed the treatment of adult DD with palpable cord by injection of collagenase *Clostridium histolyticum* (CCH). In 2011, the European Medicines Agency approved it as a safe and effective nonsurgical treatment. In 2012, a prospective multicenter trial started in Italy (Alberton et al. 2013), and in 2013, it was approved as an NHS prescription drug.

In the last 5 years, several published scientific studies have demonstrated the efficacy and tolerability of CCH in the short term in patients with Dupuytren proximal interphalangeal (PIP) joint and metacarpophalangeal (MP) joint contracture (Badalamente et al. 2015; Warwick et al. 2015). Recently the literature demonstrated its efficacy and safety if injected in two affected joints concurrently without a greater risk of adverse events, except skin laceration (Coleman et al. 2014; Gaston et al. 2015). The CCH injection has an overall recurrence at 5 years comparable with published recurrence data after surgical treatment (Felici et al. 2014; Peimer et al. 2015). The unsolved problem in DD treatment remains the contracture and stiffness of the involved joints.

The essential role of hand therapy after hand surgery is undisputed and worldwide accepted. Hand therapy makes use of a variety of techniques and devices to aid the recovery of hand function, such as passive and/or active mobilization exercises, managing of the scar tissue, and splinting (Herweijer et al. 2007). In clinical practice, the protocol should always include exercise therapy, and extension splinting is suggested after DD surgical treatment to reduce or minimize finger contracture. There is no consensus on

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how to build the device, how long to wear it in a day, and when to discontinue it.

Our experience on splinting after CCH injections considers the real benefits of using a dorsal dynamic tension-free splint, resulting in manageable volar skin without wound and retracting scars. In this way it is possible to concentrate on the tension of periarticular structures.

17.2 Material and Methods

Between 2012 and 2014, 108 patients were treated for DD with CCH. 28 cases (26%) were stage I, 55 cases (51%) were stage II, 17 (16%) cases were stage III, and 8 (7%) cases were stage IV according to the Tubiana classification. 87 patients had an MP volar cord and 21 a PIP cord. 18 were recurrences after fasciectomy (13 at MP and 5 at PIP). No treated thumbs were included in this review. All the patients received only one vial and only a cord each was treated. The terms of administration indicated by the drug company were respected in all the cases. On day one, patients received collagenase; on day two, they received progressive manipulation under local anesthesia until the cord broke in order to reach the maximum extension of the finger; then a nonremovable Zimmer finger splint was positioned. During the 3–5 successive days, the hand therapist applied a custom-made dorsal dynamic tension-free splint (Evans et al. 2002), made of thermoplastic material (Fig. 17.1). The splint allowed free movement of the wrist and the untreated fingers.

The patients were instructed to change the dressing daily or to massage the volar part in absence of skin lesions with elasticizing cream. Following the therapist's instructions, they had to free the distal anchorage ring in order to activate the involved finger immediately after the custom-made splint was applied, 20 min 4 times a day for 21 consecutive days (Fig. 17.2). Then they had to wear it only during the night for 5 weeks more. They also learned to self-adjust the tension of the distal ring, to provide progressive soft dynamization of the finger. The patients had to follow two kinesis-assisted sessions a week for the first 3 weeks after injection.

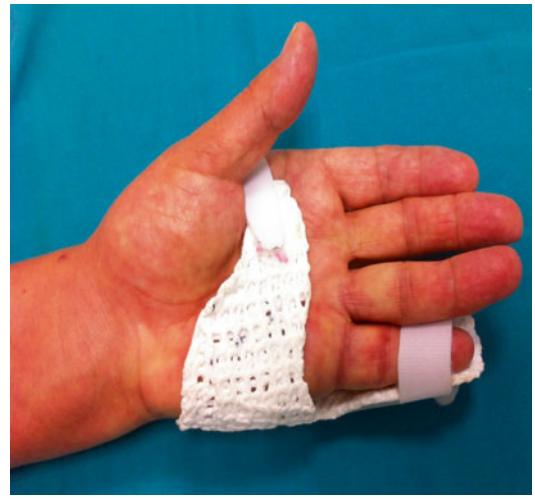

Fig. 17.1 Volar view after Dupuytren Disease of a digital cord of the fifth finger treated with collagenase of *Clostridium histolyticum*. A custom-made dorsal dynamic tension-free splint in thermoplastic material applied to the hand

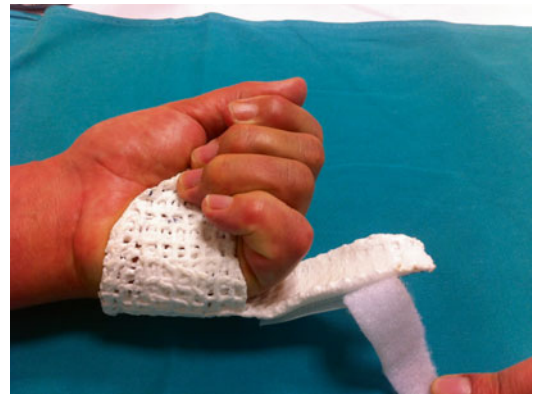

Fig. 17.2 The patient can open the distal anchorage ring to start active and passive finger movement

All the patients received several follow-up visits in the first six months after treatment.

17.3 Results

The results obtained in this trial with collagenase were fully satisfactory and aligned with those reported in literature (Warwick et al. 2015). The use of a dorsal tension-free splint was well tolerated in both MP and PIP cords. Skin problems

due to traction were not reported; the patients were instructed on how to calibrate the tension of the distal ring in order to avoid pain, flare reaction (Rivlin et al. 2014), or a complex regional pain syndrome (CRPS).

The patients who had a skin laceration due to post-collagenase manipulation could apply a volar dressing associated to the dorsal splint. They did not report any pain and all had spontaneous skin healing in 17 days on average without stitches or skin graft.

In 26 cases (24 %) revision of the splint shape was necessary for a better adaptation to the tension required. Poor tolerance to dorsal metacarpal compression caused by the splint in the first cases treated resulted in an improved splint design with a thicker padding.

No patients required a premature splint removal for intolerance. There were no cases of allergy to the thermoplastic material used, and the therapists never had to change the dorsal splint for a more commonly used volar device due to intolerance or unsatisfactory traction.

17.4 Discussion

Splinting is a commonly prescribed therapeutic modality designed to maximize the finger extension achieved from DD correction, as a result of open surgery or percutaneous fasciotomy (Kemler et al. 2012). After open aponeurectomy several factors need to be considered for a successful splinting: dressing, perioperative side effects, patient sufficiency, and scar remodeling. The scar evolution continues for up to 6 months after surgery, and splinting aims at providing low-load continuous force in order to prevent contracture recurrence.

Few studies evaluate the real efficacy of postoperative splinting and a meta-analysis of the most recent papers shows that splinting is effective for treatment of DD contracture especially when the PIP joint is involved (Larson and Jerosch-Herold 2008; Jerosch-Herold et al. 2008). Jerosch-Herold et al. demonstrated that patients receiving only hand therapy without splint after surgical approach show a higher tendency to lose finger extension for scar contracture, especially when the surgical scar crosses the MP or the PIP joints (Jerosch-Herold et al. 2008; Jerosch-Herold et al. 2011). The tension applied by the splint to the treated finger has to be low in order to avoid adverse outcomes as flare symptoms and keloid scars (Rivlin et al. 2014).

There is no proven evidence that a dorsal splint is more efficient than a volar one.

In the use of CCH for the treatment of DD, there is a high rate of minor side effects. Twenty-two percent of study patients developed skin lacerations and blood blisters after injection or after manipulation with more severe preinjection deformity showing higher risk. As reported in literature, these side effects are self-solving soft tissue distresses, and, if present, the scar is softer and more easily manageable than the scar left by an open surgery (Hurst et al. 2009). They are well-known conditions, which are not usually considered complications. Less severe preintervention contractures tend to correct better, with a lower side effect rate.

After the extension manipulation, the injected skin is softer, the finger is extended, and often cords are no longer palpable in the injection site for a length of 1–3 cm. If a skin wound occurs during manipulation, a simple thin dressing is sufficient in order to help the patient obtain immediate active and passive finger movements. Consequently, a dorsal splint is useful in the treatment of volar skin lacerations without compression to the distressed skin.

The self-management of the hand after CCH treatment is easier than after open surgery.

This procedure does not cause surgical wounds, avoiding the need to elongate scar tissue, so it is possible to concentrate on the other deeper soft tissues tending to contract: tendons and periarticular ligaments (MP and PIP). Also the patient is more willing to restore and maintain extension of the finger immediately after cordotomy with CCH, thanks to the absence of volar wounds, less pain, no fear to break the stitches, and the possibility to apply elasticizing cream to massage the skin immediately. Therefore, a dorsal custom-made dynamic tension-free splint (Fig. 17.3) results as more acceptable and can be concomitantly used with a palmar dressing.

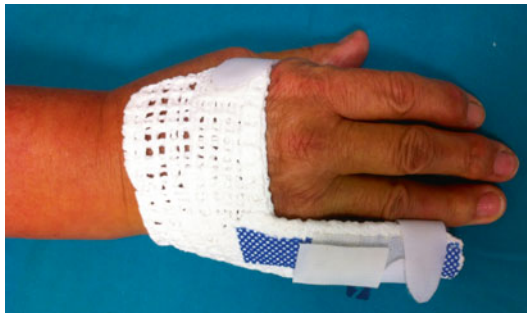

Fig. 17.3 Dorsal view of the splint

Conclusions

The use of a custom-made dorsal dynamic tension-free splint for soft tissues treatment after CCH injection for DD is effective and well tolerated by patients.

The dorsal application helps the patient to check and treat the stretched volar skin without removing the splint.

The distal ring for finger anchorage to the splint has to be closed with a light tension regulated by the informed patient, in order to transfer a progressive stretching dynamization to the soft tissues. Due to CCH injections, there was no surgical scar, which allowed a shorter period of treatment.

Conflict of Interest The authors have no conflict of interest to declare.

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18 Prospective Multicenter, Multinational Study to Evaluate the Safety and Efficacy of Concurrent Collagenase Clostridium Histolyticum Injections to Treat Two Dupuytren Contractures in the Same Hand

Marie A. Badalamente, Lawrence C. Hurst, R. Glenn Gaston, Richard A. Brown, James P. Tursi, and Ted Smith

Contents

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18.1 Introduction

In early 2010, collagenase clostridium histolyticum (CCH) injection(s), 0.58 mg, was approved by the US Food and Drug Administration for the treatment of Dupuytren contracture in adults with a palpable cord. Following injection cord rupture 24 h later was accomplished by finger manipulation in extension. Subsequently, regulatory agencies around the world also approved this treatment method as safe and effective. This study was conducted to evaluate the safety and efficacy of concurrent administration of two collagenase clostridium histolyticum (CCH) injections (each 0.58 mg) into cords in the same hand to concurrently treat two joints with Dupuytren fixed flexion contractures (FFC) with palpable cords.

18.2 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 at 56 investigative sites. Two 0.58-mg CCH doses were injected into one or two cords in

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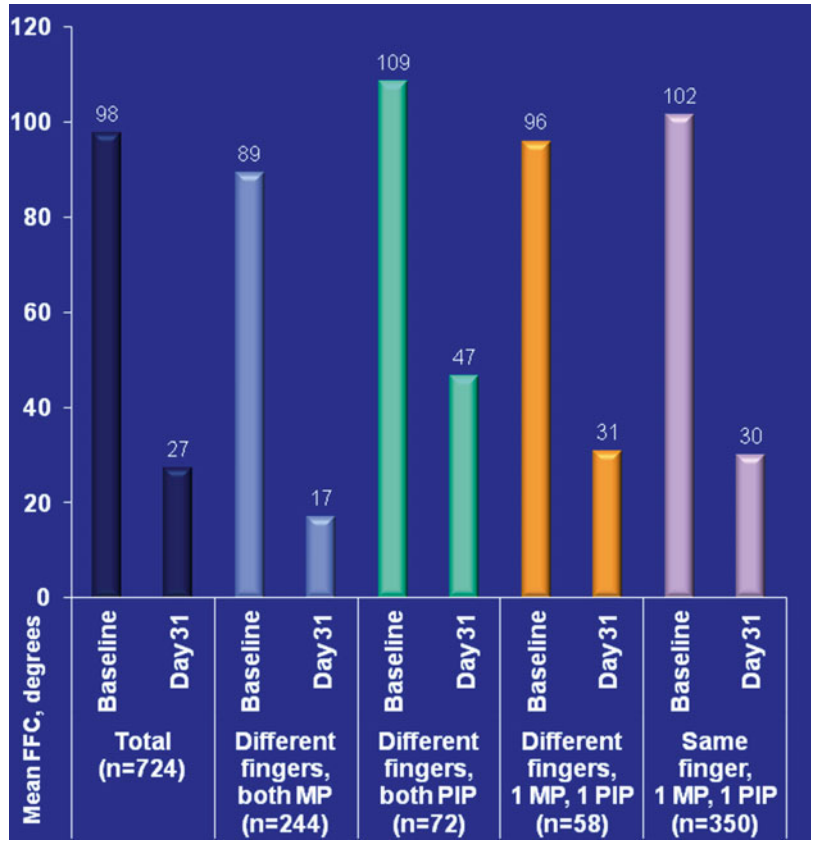

Fig. 18.1 Mean flexion contractures from baseline to day 31

the same hand (one injection per affected joint) during the same visit. Finger extension was performed 24–72 h later. Changes in fixed flexion contracture (FFC) and range of motion (ROM), rates of clinical success (FFC 0–5°), and adverse events (AEs) were summarized.

18.3 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° (Fig. 18.1). Mean total ROM increased from 90° to 156° (Fig. 18.2). Clinical success (FFC 0–5°) was reached in 64.6 % of MP joints and 28.6 % of PIP joints. The most common treatment-related adverse effects (AEs) were edema peripheral, contusion, and pain in extremity (Table 18.1). The majority of treatment-related AEs were mild or moderate in severity. Sixteen patients reported ≥1 treatment-emergent severe adverse effects (SAEs). Six patients experienced SAEs considered as 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.

18.4 Summary

- Compared with reported results of phase 3 clinical trials (Hurst et al. 2009; Gilpin et al. 2010) (using up to 3 injections/joint,

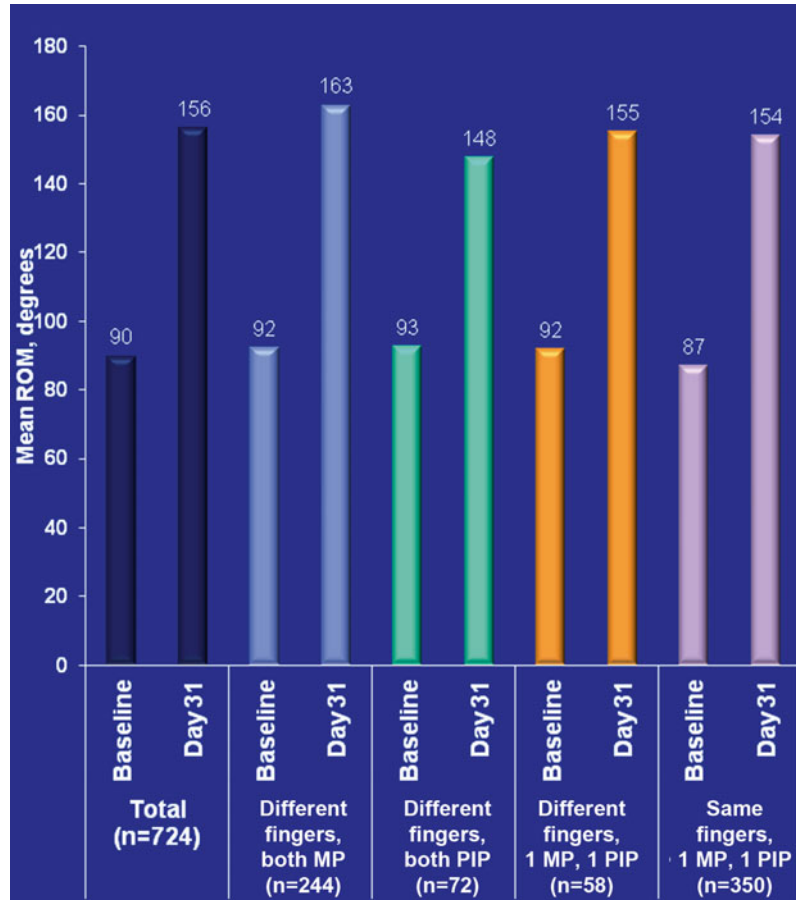

Fig. 18.2 Range of motion at baseline and day 31

Table 18.1 Most common treatment-related AEs

AE, *n* (%) (*n* = 715)	Different fingers Both MP Total (*n* = 244)	Different fingers Both PIP (*n* = 72)	Fingers 1 MP/1 PIP (*n* = 58)	Same finger 1 MP/1 PIP (*n* = 351)
At least 1 AE 680 (95.1)	228 (93.4)	71 (98.6)	55 (94.8)	336 (95.7)
Edema peripheral 552 (77.2)	186 (76.2)	56 (77.8)	47 (81.0)	271 (77.2)
Contusion 419 (58.6)	145 (59.4)	49 (68.1)	36 (62.1)	197 (56.1)
Pain in extremity 361 (50.5)	116 (47.5)	41 (56.9)	27 (46.6)	182 (51.9)
Skin laceration 160 (22.4)	40 (16.4)	16 (22.2)	8 (13.8)	96 (27.4)
Pruritus 106 (22.4)	31 (12.7)	9 (12.5)	2 (3.4)	66 (18.8)
Injection site pain 101 (14.1)	30 (12.3)	12 (16.7)	5 (8.6)	54 (15.4)
Lymphadenopathy 93 (13.0)	29 (11.9)	6 (8.3)	10 (17.2)	51 (14.5)
Blood blister 89 (12.4)	9 (3.7)	17 (23.6)	8 (13.8)	55 (15.7)

Serious AEs: 6 considered treatment-related or possibly treatment-related
1 anaphylactic reaction (resolved with treatment in emergency room)
1 tendon rupture
1 with post-procedural hemorrhage 1 with lymphangitis
1 with deep vein thrombosis and pulmonary embolism
1 with lymphadenopathy, malaise, edema peripheral, and pain in extremity
1 undefined by investigator

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.

- 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.
- The serious adverse event of possible anaphylactic reaction was treated with IM epinephrine and oral Benadryl and resolved in 4 h. The FDP rupture likely resulted from inappropriate injection technique. The tendon was surgically repaired. Care must always be taken to avoid injection of tendons, especially when injecting contractures of the PIP joint and especially the PIP joint of the fifth finger.
- Finally, the use of two concurrent CCH injections has been approved by the US Food and Drug Administration in October 2014.

Conflict of Interest Declaration

M. Badalamente and L. Hurst: Research support for this study by Auxilium Pharmaceuticals; consultants to (MB) Endo Pharmaceuticals and Actelion Pharmaceuticals; Partial Xiaflex/Xiapex royalty from BioSpecifics Technologies Corp.

L. G. Gaston: Research support for this study, speaker's bureau – Auxilium Pharmaceuticals; Consultant, royalties – Biomet; Advisor of Smith & Nephew, BME, MiMedx

R. A. Brown: Research support for this study, speaker's bureau – Auxilium Pharmaceuticals

J. P. Tursi: Former employee of Auxilium Pharmaceuticals

T. Smith: Employee of Endo Pharmaceuticals

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Collagenase: What We May Never Know (A Discussion)

19

David Warwick

Contents

19.1 Background

Clostridial collagenase histolyticum ((CCH) Xiapex, Xiaflex) has become established as one of the tools available for the treatment of Dupuytren Disease. Whilst our knowledge and experience increases with this product, there remain issues which should be addressed. This article is designed to provoke some discussion about whether or not these issues can be resolved with appropriate study.

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19.2 What We Already Know

Clinical experience and the literature on Xiapex are growing rapidly, and certain principles and points have become established:

- The technique is popular with patients and many surgeons.
- The injection is usually quite, and sometimes very, painful.
- There is a high chance of a transient but bothersome complication such as skin splitting, bruising, swelling, blistering or axillary pain (Witthaut et al 2013; Peimer et al 2013; Warwick et al. 2015b; Peimer et al. 2015a).
- There is a very low but nevertheless material risk of a tendon rupture with imperfect technique.
- Immediate correction is high especially in MCP cords (Warwick et al. 2015a, b).
- Recovery is prompt (median 4 days; Warwick et al. 2015a) and far prompter than surgery.
- Initial patient satisfaction is generally high.
- The drug is very expensive and this has inhibited its adoption in many economically strained health systems.
- The correction is better with a local anaesthetic injection, but this may increase the skin rupture rate (Warwick et al. 2015b).

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- The recurrence rate is disappointingly high (56 % at the PIP joint and 27 % at the MCP joint at 3 years, rising to 66 % and 39 %, respectively, at 5 years (Peimer et al. 2015b).
- Nevertheless, the surgical procedure in a field previously injected with Xiapex is usually not compromised (Hay et al. 2014).
- More than one cord can be injected with a higher dose without apparently an increase in the complication rate (Coleman et al. 2014; Verheyden 2015).
- The manipulation can be performed a few days after the injection, helping diary management (Manning et al. 2014; Mickelson et al. 2014).

19.3 What We Will Know

As experience with collagenase increases and as more appropriately designed studies are published, we will gradually discover the answer to important questions such as:

- How much is the risk of an allergic reaction increased either with a larger initial dose or repeated doses?
- Can a larger dose be used safely and effectively to address a thicker or longer cord?
- How well does it work for recurrence after surgery?
- How effective is it for recurrence after CCH?
- Can it be used safely in those who are anticoagulated?
- Does skin tearing improve outcome by the regeneration of new skin?
- What is the recurrence rate in the "real world" outwith the initial index studies (Cord I and II)?
- Is splinting required after CCH injection?
- Does an individual's satisfaction deteriorate over time as recurrence appears?
- Will the current increasing enthusiasm for CCH plateau and then fall as its proper place within the armamentarium of treatment for DD is established by clinical experience, research and consensus? (Scott's parabola; Scott 2001; Jupiter and Burke 2013)

19.4 What We May Never Know

One shortcoming of CCH is that it has not been thoroughly compared with existing treatments such as percutaneous needle fasciotomy (PNF), limited fasciectomy (LF) or dermofasciectomy and grafting. Indeed some healthcare systems will not consider CCH without reliable comparative data from randomised controlled trials (RCTs). The UK National Institute for Health Care Excellence (NICE) has announced in 2015 that CCH can only be used in a research study. In an environment in which "evidence-based medicine" is a significant force, there may be, in the author's view, an unrealistic expectation on the potential for RCTs to answer all pertinent questions.

There is no doubt that properly designed and funded RCTs are needed to establish more facts about CCH, but there are limitations that should be carefully considered in this field.

19.4.1 Heterogeneity of Disease

DD has a diverse presentation and it is not rational to expect one treatment to be suitable for all types. Cords can range from "twigs" to "logs". Very fine subcutaneous cords especially at MCP level are eminently suitable for PNF; it would not be appropriate to design a trial to compare PNF and CCH. These cords are eminently suitable for PNF which is cheaper and less prone to regional complications. However, very broad cords are not suitable for PNF, are more likely to be suitable for CCH yet can always be addressed with surgery. Cords close to the PIP joint can be safely addressed with CCH, yet many would be concerned about the neurovascular risk with PNF. Some dense scarred recurrent cords, cords with skin involvement or those in patients with a diathesis are probably more suitable for dermofasciectomy than LF, CCH or PNF. So an RCT would have to exclude perhaps the majority of cords due to heterogeneity. As the exclusion rate rises, the generalisability of the study diminishes.

19.4.2 Learning Curve and Experience

One advantage of CCH is the relative ease of use, even in quite broad cords or cords close to the PIPJ. The learning curve is low. PNF is not widely used in many healthcare systems, and the technique might have an unfavourable outcome compared with CCH if undertaken by a novice; furthermore, if the PNF is performed well by an experienced operator in an RCT, the results of that trial will not be reliably generalisable to the novice who wishes, or is prompted, to transfer the result of that trial to their own practice.

19.4.3 Absent Equipoise

An RCT can only be undertaken ethically if both clinician and patient have equipoise for both treatments. In the author's experience, approximately 4/5 patients requesting CCH would not readily agree to surgery. They are drawn to CCH because it is a non-surgical option. A considerable proportion, even if counselled that their cord would be suitable for PNF and that CCH has an appreciable complication rate, still choose CCH, attracted by the concept of a "surgical drug that removes disease". So recruitment will be impaired by patient bias. Furthermore, different surgeons feel that different cords are suitable for different treatments and so they may be biased as well in their consideration within a trial as to cords that are suitable for one or another of the treatment options.

19.4.4 Suitable Outcome Measures

The most appropriate outcome measure in DD research has not yet been established. As discussed elsewhere in this book, *angular deformity* does not correlate too well with function. *Generic upper limb scores* such as DASH are not specific enough (Budd et al. 2011). *DD specific functional* scores such as the Southampton scheme (Arvind et al. 2014) and URAMS (Beaudreuil et al. 2011) have not been broadly validated (Rodrigues et al. 2015).

Expense as an outcome measure can be spurious. Whilst CCH is quite expensive, the cost can be retrieved if the quick recovery leads to prompt return to earning (and taxpaying) for the self-employed or to the economic contribution of the employed. PNF is cheap but the high recurrence rate means that treatment costs will be probably be repeated. These societal costs are not readily factored in the healthcare cost to the payer of healthcare.

Complications are an important outcome measure; indeed if the primary outcome (e.g. angular deformity) is equivalent in an RCT, the value of secondary outcomes such as complications or cost becomes more important as a discriminator. However, different complications occur in different treatments. Risk is not calculated by rate alone but in a matrix of both frequency and severity (Fig. 19.1). One cannot compare nerve damage (a risk in surgery but not in CCH) with allergic reaction (a risk in CCH but not surgery); one cannot compare a skin blister in CCH (which is very common but short lived) with CRPS in surgery (which is rather rare but can be a significant and permanent disability).

19.4.5 Recurrence as an Outcome Measure

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. So even if the recurrence rate after CCH and especially PNF is very high, if that recurrence is easily, effectively, safely and relatively cheaply treated, then the value of recurrence as an outcome measure is diminished.

In contrast, recurrence after previous LF is a complex and more risk-prone procedure due to a scarred field compounding the recurrent DD. So a lower recurrence rate after primary surgery may be offset by the complexity of treating that recurrence. Liberal use of dermofasciectomy as the first

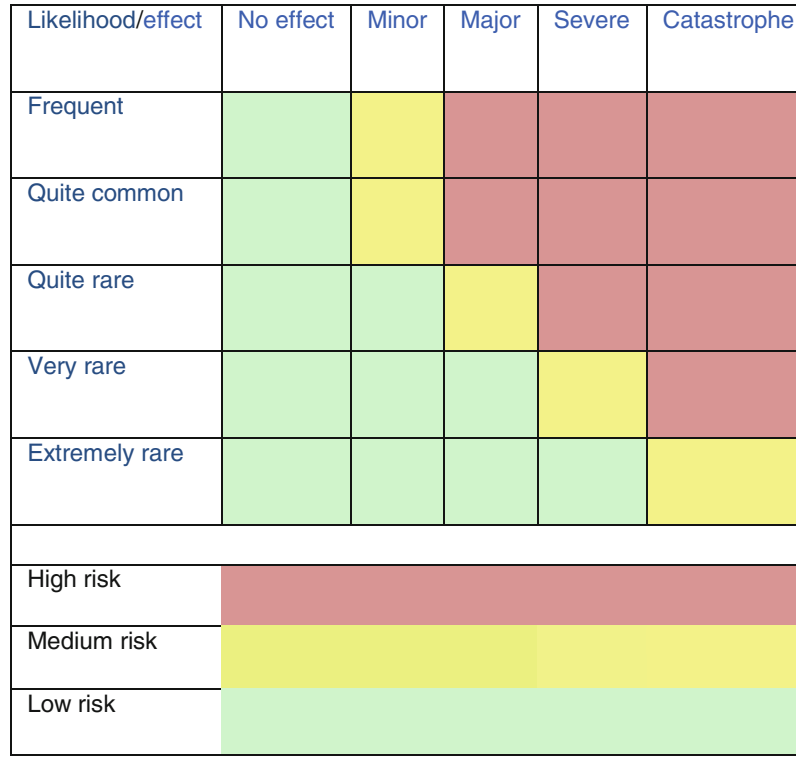

Fig. 19.1 Risk matrix

operation of choice for DD, whilst being a little more complex, has a much lower recurrence rate so overall may be a more cost-effective procedure and, by minimising the chance of a more hazardous second operation, be an overall safer option.

19.4.6 Funding

An RCT requires funding. The cost is unlikely to be supported by a pharmaceutical company (which might be concerned that the drug would fair unfavourably, particularly if the study is designed to minimise the issue of heterogeneity by including only those cords suitable for either PNF or CCH). A state-funded trial would, in the absence of a robust protocol with the issues discussed in this chapter, be unlikely to receive funding in competition for the same funds towards a more generalisable study.

19.4.7 Blinding

A randomised trial should, whenever possible, be blind to the procedure and assessment outcome from the perspective of both the patient and the investigator. This would present challenges when comparing PNF, CCH and LF. The original RCTs that lead to licencing of CCH used a placebo but there is no further need for a placebo study. A sham operation or sham PNF is not possible. The outcome measures could however be blinded from the investigator (but not patient) if, for example, a glove covers the scars which would reveal if surgery had been performed.

19.4.8 Duration of Follow-Up

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 probably take two years to set up and fund, three years to recruit, five years to follow-up and two years to analyse and publish, so twelve 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.

Conflict of Interest The author has been a paid consultant to Pfizer and SOBI (European distributors of Xiapex) and Actelion (Australian distributor of Xiaflex.) He has received travel support, accommodation and honoraria on several occasions in relation to advising on the drug and giving presentations to learned societies and other groups. He has not been paid or received any other support in relation to the International Dupuytren Symposium or to this chapter.

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Controversy: Comparison of the Literature on PNF and CCH as Minimally Invasive Treatment Options for Dupuytren Disease

20

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20.1 Introduction

At present, two effective minimally invasive treatment modalities are available for the treatment of Dupuytren Disease: percutaneous needle fasciotomy (PNF), also named needle aponeurotomy (NA), and injection of collagenase derived from *Clostridium histolyticum* (CCH). In this chapter an objective comparison will be presented based on available scientific literature and personal experience. Both methods will be compared on the following aspects: indication, techniques and disposables needed, costs, complications, comparison of aftercare and discomfort, time off work, effectiveness of the intervention and durability of the result, patient satisfaction, treatment of recurrences and ease of salvage surgery.

20.2 Comparing PNF and Collagenase Injection

20.2.1 Indication for Application of the Techniques

The indication for both techniques is a well-defined cord that is responsible for a contracture in any of the joint digits of the hand. PNF can be employed at any level in the hand (Eaton 2011). CCH use is off-label if administered beyond a point 4 mm distal to the palmodigital crease or the thumb (https://www.xiaflex.com/hcp/dupuytrens-contracture/about-xiaflex/

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patient-selection/) (Hurst et al. 2009). This means that according to label, PNF has a wider application possibility.

20.2.2 Need of Additional Drugs and Disposables

Both techniques can be employed in an outpatient clinic environment. By some a treatment room is preferred, while in very complex cases for PNF operating theatre setting may be desirable, with related financial implications. However, in most cases for PNF, costs made are only for the following disposables: 10 cc syringe, a few 25 gauge needles, 5 cc lidocaine 1 % + adrenaline (1:100,000), a few sponges and a small bandage. Patients are usually treated in supine position with their arm on a sideboard. The portals for access to the cords are marked and small aliquots of local are injected to numb the skin. Cord division is attempted starting distally and portals are preferably placed at spots where the skin is non-adherent to the cords. Cords are divided using a pivoting or sweeping motion, taking care not to damage the adjacent tendons or nerves. If the pathology is fixed to the skin, it can be released or "cleared", to diminish the chance of skin tearing (Eaton 2011). Typically, treatment takes 5–10 min per ray.

For CCH application and for the cord rupture procedure which is performed at least 24 h post-injection, more or less the same disposables are necessary. In addition CCH comes as a powder in a vial and has to be reconstituted using the provided diluent. This takes a few minutes only. The drug is usually administered at three locations along the cord using a 1 cc hubless syringe. Local anaesthesia is used to numb the injection area during cord disruption (Hurst et al. 2009). Very recently experience has been reported with treatment of more than one contracture using two vials of CCH at the same time (Coleman et al. 2012).

20.2.3 Cost

CCH in the Netherlands costs €750 per vial. In the USA the drug is considerably more expensive. These costs make treatment with CCH much more expensive than PNF, unless done in an operating theatre.

20.2.4 Complications

The reader should realize that the initial phase III studies in which CCH was tested against placebo were two very rigidly controlled and audited studies, CORD I and CORD II, in which very strict definitions of success were used, while all adverse and serious adverse events were monitored (Gilpin et al. 2010; Hurst et al. 2009). Most studies that report on facets of PNF have probably not been designed, executed and monitored as rigidly. This difference very likely influenced the report of complications.

Serious adverse events following PNF as well as following CCH injection are rare. The overall complication rate following PNF is 20 % (Crean et al. 2011). Lermusiaux reported 5 tendon injuries in 60,000 PNF (Lermusiaux et al. 2001). Badois reported dysaesthesia in two percent of 138 cases treated with the same technique (Badois et al. 1993). Foucher reported one digital nerve injury in 165 cases of PNF (Foucher et al. 2003). In the retrospective study of Pess on over 1,000 fingers treated with PNF, complications were rare except for skin tears, which occurred in 3.4 % (34) of digits (Pess et al. 2012). They reported one case of digital nerve injury (0.1 %). Van Rijssen et al. reported no serious adverse events following PNF but almost 50 % skin fissures and 7 % of dysaesthesias (van Rijssen et al. 2006).

Hurst reported three treatment-related SAEs following CCH treatment in 308 patients: two tendon injuries and one case of complex regional pain syndrome (Hurst et al. 2009). Gilpin found a flexor pulley injury and a case of diminished sensibility in a cohort of 66 cases (Gilpin et al. 2010).

At the same time, the incidence of adverse events, such as bruising, hematoma formation, pain, swelling, skin laceration, etc. is very high (97 %) if monitored carefully (Hurst et al. 2009).

From this comparison one might conclude that treatment with CCH is hampered with much

Table 20.1 Complications

	Author				
	Lermusiaux et al. (2001)	Foucher et al. (2003)	Van Rijssen et al. (2006)	Pess et al. (2012)	Hurst et al. (2009)
	PNF	PNF	PNF	PNF	CCH
SAE					
Tendon injury	0.01%				0.6%
Pulley injury					
CRPS		0.5 %			0.3 %
Nerve injury		0.5 %		0.1 %	
AE					
Skin fissures	2 %	10 %	48 %	3 %	
Temporary dysaesthesia	0.8 %	3 %	7 %	1 %	
Pain	0.3 %	6 %			
Injection site pain					32 %
Upper extremity pain					31 %
Infection	0.2 %				
Haematoma	0.2 %				
Oedema		0.5 %			72 %
Bleeding		0.5 %			
Contusion					51 %
Injection site haemorrhage					37 %
Injection site swelling					21 %
Tenderness					27 %
Ecchymosis					25 %
Pruritus					16 %
Skin laceration					11 %
Lymph node affection					21 %
Erythema					6 %
Blister					5 %
Others					24 %

SAE treatment-related serious adverse event, *AE* treatment-related adverse event; others included all complications each occurring in less than 5 % of cases: axillary pain, arthralgia, vesicles at injection site, inflammation, blood blisters, joint swelling, headache and swelling

more complications, but it is conceivable that AEs were underreported in studies on PNF. Following CCH injection more SAEs have been reported (Table 20.1).

20.2.5 Aftercare and Discomfort

Following PNF, the treated area is covered with a small bandage that can be removed by the patient within a day, after which almost all activities can be resumed. If a skin fissure has occurred, a Band-Aid may be needed a bit longer. Splints are not used routinely by everybody. Pain after PNF is rare.

Hands treated with CCH in the initial studies have been immobilized in a bulky dressing until cord release. Thereafter a removable splint was fitted. With increased experience these measures have not been found necessary to obtain a good

result. Hands are usually swollen and painful for a number of days and patients return to normal activities after 4 days (Warwick et al. 2015). Axillary lymphadenopathy can occur and be painful for a few days too.

20.2.6 Time Off Work

After PNF as well as after CCH treatment, the general advice to patients is to refrain from heavy labour until 2 weeks after treatment (Pess et al. 2012). Exact figures about time to return to work are not available.

20.3 Outcome of Both Procedures

20.3.1 Early Outcome (Table 20.2)

Unfortunately, the way in which results of PNF and CCH have been reported in the general body of the literature has varied. For instance, Foucher et al. as well as van Rijssen et al. used reduction of total passive extension deficit (TPED) per ray as a primary outcome measure, whereas Hurst et al. and Gilpin et al. focused on the efficacy of treatment per joint and used definitions for clinical success (reduction of contracture to 0–5°) and clinically significant improvement (at least 50 % reduction) (Badalamente and Hurst 2007; Foucher et al. 2003; Gilpin et al. 2010; van Rijssen and Werker 2006; van Rijssen et al. 2006). This makes comparison of these studies quite difficult.

Pess et al. in a large retrospective study on PNF in over 1,000 fingers were the only ones who reported using the same methodology as the groups studying the efficacy of CCH (Pess et al. 2012). They were able to correct MCP joint contractures in an average of 99 % and PIP contractures in an average of 89 %, which is very high. Needle aponeurotomy led to successful correction to 5° or less contracture immediately post-procedure in 98 % (791) of MP joints and 67 % (350) of PIP joints.

In their 5-year follow-up study on the efficacy and durability of PNF versus LF, van Rijssen et al. in their discussion reanalyzed their results using the same criteria as Pess et al. They found that 55 % of the treated MCP joints in the percutaneous needle fasciotomy group reached clinical success. In the proximal interphalangeal joint, the corresponding figure was 26 % following percutaneous needle fasciotomy. This shows that the results achieved by Pess et al. were much better.

Witthaut presented the following pooled data of two open-label CCH studies: Dupuytren cords affecting 531 MCP and 348 PIP joints in 587 patients were treated with CCH injections. Clinical success was achieved in 57 % of treated joints using 1.2 ± 0.5 (mean ± SD) injections per cord. More MCP than PIP joints achieved clinical success (70 % and 37 %, respectively) or clinical improvement (89 % and 58 %, respectively). Less severely contracted joints responded better than those more severely contracted (Witthaut et al. 2013). In a subsequent study, the results for PIP contractures of 4 phase 3 studies have been clustered. A total of 506 patients received a mean of 1.6 injections in 644 PIP joint cords. Clinical success and clinical improvement occurred in 27 and 49 % of PIP joints after one injection and in 34

Table 20.2 Comparison of early outcome

	Pess et al. (2012)	Van Rijssen et al. (2012b)	Nydick et al. (2013)		Witthaut et al. (2013)	Badalamente et al. (2015)
	PNF	PNF	PNF	CCH	CCH	CCH
Clinical success			67 %	56 %		
MCP	98 %	55 %	81 %	64 %	70 %	
PIP	67 %	26 %	50 %	42 %	37 %	34 %
>50% improvement						
MCP					89 %	
PIP					58 %	58 %

and 58 % after the last injection. Patients with lower baseline severity showed greater improvement, and response was comparable between fingers, as were improvements in range of motion (Badalamente et al. 2015).

There is only one study that retrospectively compares the outcomes of PNF and CCH treatment (Nydick et al. 2013). Clinical success was accomplished in 35 of 50 joints (67 %) in the PNF group and in 19 of 34 joints (56 %) in the collagenase group.

From these data, it can be concluded that one PNF session for a PIP joint contracture is at least as effective as one CCH injection and that PNF at MCP level in one study is more, in one study equally effective and in one study less effective than CCH treatment.

20.3.2 Patient Satisfaction

Satisfaction is an ill-defined characteristic in Dupuytren treatment. Notwithstanding this, at 6 weeks following PNF satisfaction has been reported to be higher than following limited fasciectomy, most likely because the burden of the procedure is less and recovery following PNF is quicker (van Rijssen et al. 2006). Medjoub reported satisfaction following PNF in 75 % of cases (Medjoub and Jawad 2013). Treatment with CCH led to satisfaction in 92 % of cases (Witthaut et al. 2013). In the comparative study of Nydick et al., satisfaction was similar between the two groups (Nydick et al. 2013).

20.3.3 Durability of Results

Durability of the results is the opposite of recurrence, and the reported percentages vary very much depending on the definition used (Kan et al. 2013; Werker et al. 2012). Foucher used the definition increase of TPD of more than 30° compared to the post-op result and reported a recurrence rate of 58 % following PNF after 3 years (Foucher et al. 2003). In line with this, and using the same definition, van Rijssen et al. reported a recurrence rate of 65 % after 3 years and of 85 % after 5 years (van Rijssen et al. 2012a, b). In addition they found a significant positive correlation between age at time of treatment and occurrence of recurrence.

Pess et al. used the definition increase of PED at the treated joint of 20° and found at final follow-up, 3 years following treatment, that 72 % of the initial correction was maintained for MCP joints (28 % recurrence) and 31 % for PIP joints (69 % recurrence). The difference between the final corrections for MP versus PIP joints was statistically significant, which is a common finding for all treatment modalities. When comparing the final results of patients age 55 years and older versus under 55 years, they found – similar to van Rijssen et al. – a statistically significant difference at both MP and PIP joints, with greater correction maintained in the older group.

In CCH studies Peimer et al. used the same definition of recurrence as used by Pess (Peimer et al. 2013, 2015). The 3-year data for the successfully treated joints were as follows: Of the 623 CCH-treated joints (451 MCP, 172 PIP), 35 % (217 of 623) recurred (MCP 27 %; PIP 56 %). Of the 301 CCH-treated joints that were partially corrected in the original study, 50 % (150 of 301; MCP, 38 % [57 of 152]; PIP, 62 % [93 of 149]) had nondurable response. At year 5, 47 % (291 of 623) of successfully treated joints had recurrence (39 % of MCP and 66 % of PIP) (Table 20.3).

Comparison of the 3-year results of Pess et al. and Peimer et al. shows that results of PNF are more durable. The 5-year results of van Rijssen et al. unfortunately cannot be compared to those of Peimer et al. since they used different definitions.

20.4 Subsequent Treatment

20.4.1 Efficacy of Subsequent Treatment with the Same Treatment Modality

Van Rijssen and Werker have reported that results of PNF for recurrent disease are similar to those of primary PNF (van Rijssen and Werker 2012).

Table 20.3 Durability of results/recurrence

	Foucher et al. (2003)	Van Rijssen (2012a, b)	Pess et al. (2012)	Peimer et al. (2013)
Recurrence	PNF	PNF	PNF	CCH
>30° increase in TPED 3 years	58 %	65 %		
>30° increase in TPED 5 years		85 %		
>20° increase PED MCP 3 years			28 %	27 %[a]; 38 %[b]
>20° increase PED PIP 3 years			69 %	56 %[a]; 62 %[b]

[a]Recurrence percentage in successfully treated joints
[b]Recurrence percentage in joints in which at least 50 % correction had been achieved. For references see text

This book contains a chapter of Vlot & Werker in which the results of PNF for second, third and fourth recurrences are described. Although the series is small, the authors were able to conclude that efficacy of third and fourth PNF again was similar to previous PNF treatment. A fifth attempt became less fruitful.

Peimer et al. reported that of 105 secondary interventions performed in successfully treated joints, 47 % (49 of 105) received fasciectomy, 30 % (32 of 105) received additional CCH and 23 % (24 of 105) received other interventions. No specific problems were encountered in the CCH retreated group (Peimer et al. 2015). In a personal communication, Dr. Peimer informed me that the efficacy of retreatment has been investigated in a series of 51 cases of which 57 % achieved clinical success and 29 % achieved a clinically significant improvement.

20.4.2 Ease of Salvage Surgery Following Previous Minimally Invasive Treatment

Little has been written about this subject following PNF. My personal experience is that in general surgery is not much more difficult than in virgin cases, although it seems that more structures are affected and thickened. Two studies have addressed the topic of salvage surgery after CCH treatment (Eberlin et al. 2015; Hay et al. 2013). Hay et al. asked participants in collagenase studies to report their experience. Most of these reported that surgery had been similar in difficulty as in virgin cases. Eberlin et al. found surgery significantly more difficult, with disruption of normal architecture and scarring in all cases.

Conclusion

- At present there is only one small retrospective comparative study of PNF versus CCH available.
- CCH studies have been designed and monitored more rigidly than PNF studies. As a result more AE have been reported after CCH. SAE are infrequent for both.
- CCH treatment is more expensive.
- One PNF session is at least as effective as one CCH injection.
- Comparison of the 3-year results of studies that used the same definition of recurrence shows that results of PNF are more durable.

Conflict of Interest Declaration The author has participated in an advisory board meeting for Pfizer Ltd and Sobi Ltd. He also was a trainer for Pfizer in the use of CCH.

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Part V

Percutaneous Needle Fasciotomy (PNF)

Charles Eaton and Paul Werker,
supported by Bert Reichert

Tips and Pearls for PNF and Collagenase: A Ten-Year Personal Experience

21

Gary M. Pess

Contents

21.1 Introduction

There is no "cure" for Dupuytren contracture, no matter what treatment is chosen (Bayat and McGrouther 2006). When performing minimally invasive procedures for Dupuytren contracture, *treat early*. Since minimally invasive treatments have a lower morbidity and risk, the old paradigm of waiting for a Metacarpophalangeal or Proximal interphalangeal contracture of 30° does not pertain. The highest efficacy and lowest recurrence rates are in patients with the early contracture and minimal arthrofibrosis of the PIP joint. If a contracture recurs, minimally invasive treatments should be repeated early.

Prior to performing any procedure, a diagram of the hand is used to chart nodules, cords, previous surgical incisions and skin grafts, range of motion, and degree of contracture. Skin creases should be avoided for both needle insertion and CCH injection. The ideal locations for CCH injections and NA insertion are areas where the cord is maximally bowstringed, which increases the distance between the cord and the flexor tendons and neurovascular bundles. Supple skin, when available, is optimal for placement. Only pathologic cords are released. Scarred and contracted skin from previous open surgery and skin grafting are not treated (Fig. 21.1).

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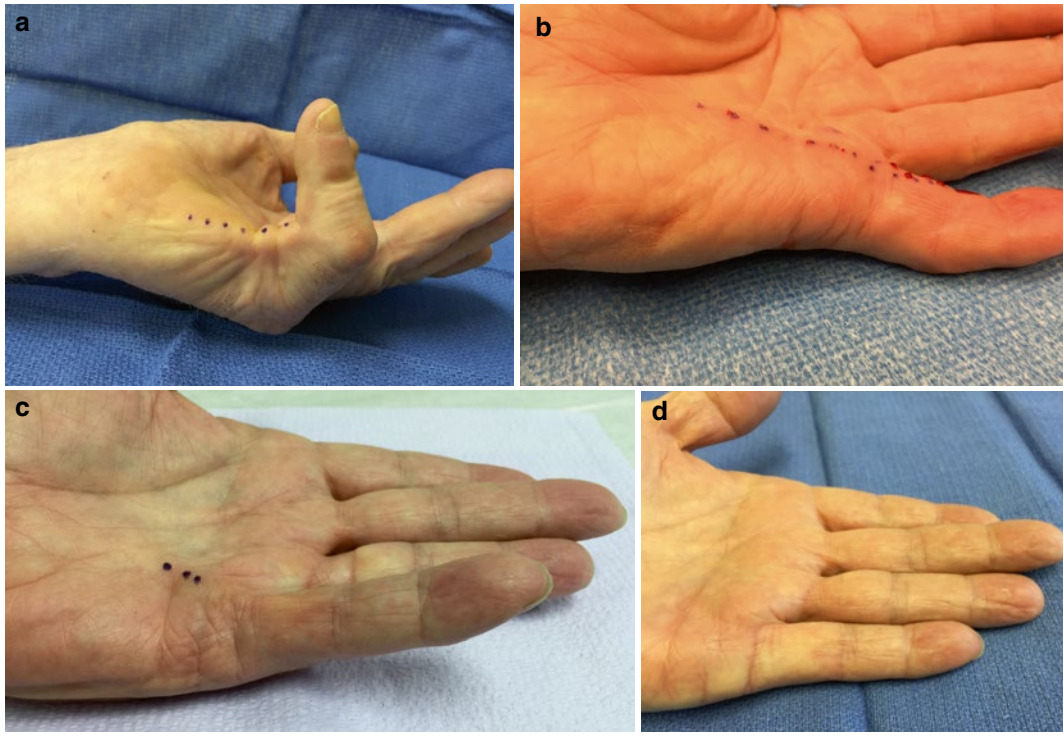

Fig. 21.1 The area of maximum bowstringing is the best location for PNF portals and for collagenase injection. (**a**) Pre-PNF, (**b**) post-PNF, (**c**) pre-CCH, (**d**) post-CCH

21.2 Technique: Percutaneous Needle Fasciotomy (PNF)/ Needle Aponeurotomy (NA)

Percutaneous needle fasciotomy is performed in an outpatient treatment room under local anesthesia with the patient recumbent (Pess et al. 2012). The patient's hand is prepped with antiseptic solution. Portal sites are carefully chosen between skin creases in areas of definite cords and are marked with a surgical marker. The injection sites may need to be modified after releasing the MP joint. The center of the cord is normally used as the needle entrance site, but 2 parallel insertion sites, radial and ulnar, may be used for wider cords >5 mm (Fig. 21.2; Eaton 2011).

Intradermal anesthesia is performed with <1 cc lidocaine 1 % plain injected in the area of the palmar portals, prior to the release of any cords. Only the dermis is penetrated, and injection is performed as the needle is withdrawn. Conscious sedation is an option for patients with a high level of anxiety.

A 5 cc syringe is filled with 3 cc lidocaine 1 % plain and 1 cc methylprednisolone acetate injectable suspension 40 mg (Depo-Medrol, Pharmacia & Upjohn Co., New York, NY). Corticosteroids are not used for patients with diabetes mellitus. Short 25-gauge, 16-mm (5/8-in) length needles are used exclusively (Lermusiaux and Debeyre 1979). Use of larger needles is not recommended. A tourniquet is not applied. Patients are asked to stop anticoagulation, if possible, but blood thinners are not considered a contraindication to the procedure.

Each time a portal is entered, 0.1 cc of the lidocaine/corticosteroid mix is injected into the local area, and the needle is used as a scalpel to release the cord at multiple levels. Beginning the release proximally and progressing in a proximal to distal direction are recommended. While releasing the contracture in the palm, some of the PIP joint contracture may release as well. It is easier to place the needles between the proximal digital crease and the middle finger crease once the MP joint has been extended.

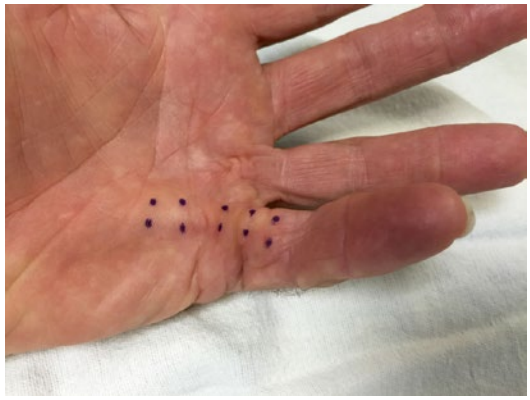

Fig. 21.2 Two parallel insertion sites are used for wide cords >5 mm

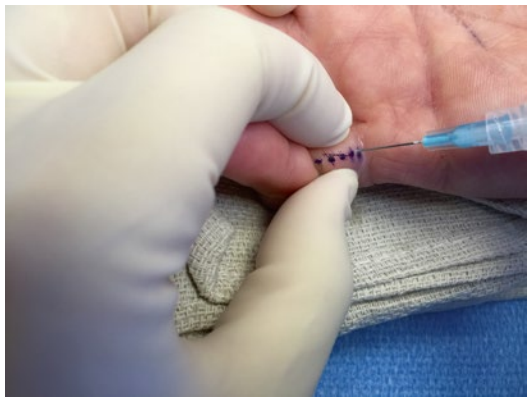

Fig. 21.3 Pinch and poke technique for PNF

A "pinch and poke" technique is employed. The cord is palpated and then pinched between the fingertips (Fig. 21.3).

The needle is aligned perpendicular to the cord. The finger is flexed and extended immediately after each needle insertion to confirm that the needle is not placed within the flexor tendon. Insertion portals are made at the areas of maximum bowstringing of a palpable cord. Areas farthest from the neurovascular bundle are selected, and the patients are constantly asked if they feel any electric shocks. Portals are spaced 5 mm apart, and skin creases are avoided. Care is taken to not push the needle in too deep. Most cords are less than 4 mm from the skin, so the needle can remain fairly superficial. The distance between hub of the needle and the skin is watched closely at all times.

To confirm a good portal site, apply traction and look for blanching (Bayat and McGrouther 2006). If the diseased cord is tighter than the skin, the skin will usually not blanch with traction. Blanching may indicate that the skin is contracted, and there may not be an underlying cord present to release. Blanching will advance distally when the underlying cord has been adequately released.

Three maneuvers are used: *perforate*, *slice*, and *clear*. An up-and-down *perforation* of the cord is performed with the needle oriented vertically. A gentle pendulum side-to-side *slicing* motion is used with the needle tip perpendicular to the cord's longitudinal axis. Division of the cord progresses from superficial to deep. It can sometimes help to push the cord against the needle while slicing. The three-dimensional anatomy of the cord should be kept in mind at all times. In areas of pitting, a tangential *clearing* motion is employed to separate the cord and nodule from the dermis. This helps to lower the incidence of skin tears. A crackly feeling is noted as the fibers are released. The needle should be changed frequently to maintain sharpness (~8–15 fresh needles per finger). Gentle extension tension is placed on the cord during the release, and then passive extension is used to rupture the cords. A pop may be heard or felt. The finger is then manipulated in abduction, adduction, pronation, and supination to release all cords. Unaffected adjacent fingers should also be manipulated, since this can help disrupt any residual cords.

Natatory cords are released by orienting the needle parallel to the longitudinal axis of the finger, perpendicular to the transverse axis of the cord (Fig. 21.4).

The cord is then released with a slicing motion, moving proximally to distally. The released cord is massaged to help disrupt remaining deep fibers. Massaging is also useful for narrow lateral cords.

After completing the release distally, the palm and finger are assessed for residual cords. Each of these cords is released, again working in a proximal to distal direction. A PIP joint contracture may still persist even after all cords are released. There is often a non-palpable central cord preventing release of the PIP contracture.

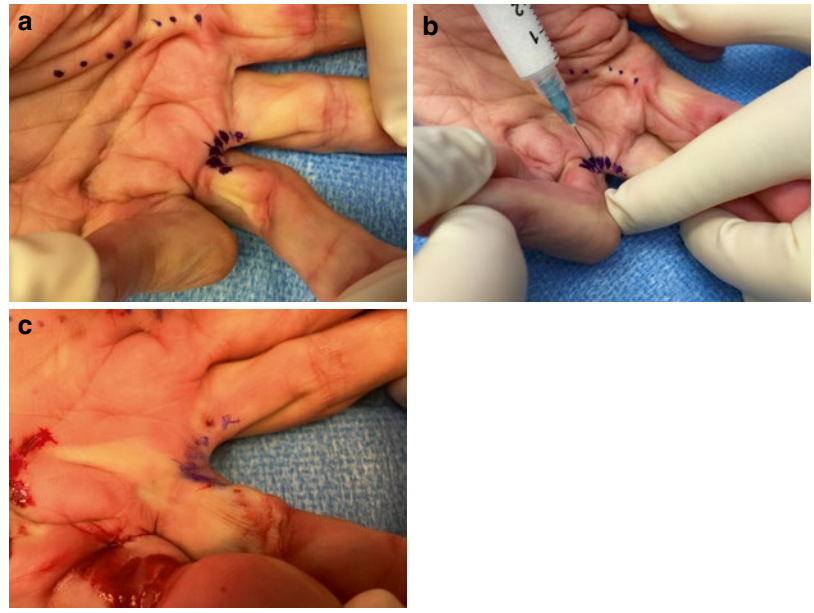

Fig. 21.4 Natatory cord released by aligning needle parallel to the longitudinal axis of the finger. (**a**) Pre-PNF, (**b**) PNF, (**c**) post-PNF

A palmar release of this cord can be performed in the midline, proximal to middle finger crease. It is critical to stay very superficial and avoid entering the flexor tendon sheath.

In patients with severe PIP joint contractures, a nerve block (wrist or digital) and/or PIP joint injection with lidocaine 1% plain is used for supplementary anesthesia. This is performed after PNF is completed to help reduce pain during the extension procedure. After all possible cords have been released, nodules are injected with the mixture of lidocaine and corticosteroid (Morhart 2015).

A light dressing with gauze bandage is applied, and removal of the bandage is allowed that evening. A splint is fitted immediately post-procedure, and night use is recommended for three to four months. Even though a splint is recommended, there is no scientific evidence supporting the use of a post-procedure splint (Henry 2014). Patients are instructed to exercise at home 5–10 min twice a day for 4 weeks. Written instructions are provided, including specific active range of motion exercises in flexion, extension, abduction and adduction, and gentle passive stretching. It is recommended that patients avoid heavy grasping for the first 2 weeks. Therapy is not needed in most instances. Hand therapy with splinting can be ordered for residual contractures and to treat PIP joints that have regained full passive extension but have a residual active extension lag (central slip laxity) (Skirven et al. 2013).

21.2.1 Tips and Pearls

Author's Tips and Pearls

Percutaneous Needle Fasciotomy

Flex and extend the finger after each needle insertion to confirm needle not in flexor tendon.

Maintain tension on cord.

The needle is aligned with the bevel perpendicular to cord.

Release perpendicular to the longitudinal axis of the cord.

Change needles frequently.

Choose areas of maximum bowstring for insertion. Select areas farthest from NV bundle.

Communication with patient is necessary – repeatedly ask patient if they feel electric shocks.

Usually center of cord, but side by side portals for thick cords >5 mm.

Release proximally to distally, allowing easier and safer release of PIP joint.

Manipulate finger in extension, adduction, abduction, pronation, and supination.

Manipulate unaffected adjacent fingers too.

Massage cords with thumb to help disrupt cord (especially useful for narrow lateral cords and natatory cords).

Release the non-palpable central cord for residual PIP joint contractures.

Inject the PIP joint for anesthesia prior to manipulating severe contractures.

21.3 Technique: Collagenase/ Xiaflex/Xiapex

21.3.1 Injection Procedure

Injection of CCH is performed in an outpatient treatment room. The patient may be sitting or recumbent. When more than one finger is affected in the same hand or multiple cords are present contracting multiple joints, 2 full doses of CCH may be used (Gaston et al. 2015). Injection sites are carefully chosen, between skin creases, in areas of definite cords and are marked with a surgical marker. It is critical to find the best areas to release the cords. Anticoagulant therapy (except aspirin 150 mg or less) is labeled as a contraindication to CCH.

For an MP joint contracture, the best area to inject is usually between the proximal palmar crease and distal palmar crease and/or between the distal palmar crease and the proximal finger crease. When a natatory cord is also present, a web space injection is necessary.

MP and PIP combined contractures are very common. The best areas to inject are proximal to the proximal finger crease (PFC) and just distal to the proximal finger crease. This can be done in a longitudinal fashion proximal to distal or T-shaped with the transverse limb just distal to the proximal finger crease (Fig. 21.5).

For PIP joint contractures, inject both the radial and ulnar cords at the same time just distal the proximal finger crease. When injecting distal to the proximal finger crease, make sure the injection is performed in the safe zone, within 4 mm of the proximal finger crease and no more than 2–3 mm deep. For wide cords distal to the proximal finger crease, inject transversely into the cord. For little finger PIP contractures, inject both the radial cord and abductor digiti minimi cord (when present). It is important to inject both the radial and ulnar cords to achieve release of the contracture (Fig. 21.6).

Super Y cords (which contract nonadjacent fingers) and Y cords (which contract adjacent fingers) can be injected proximally at the branching point and distally into both limbs. Even with only one dose of CCH, multiple joints may be released at the same time.

Thumb contractures can be due to a radial or pretendinous cord contracting the MP joint and a distal commissural cord contracting the first web space. These cords are usually thicker, but do respond to CCH injection. For a commissural cord, inject circumferentially and transversely on the palmar side to assure release.

CCH is supplied as a sterile, lyophilized powder (white cake) in a single-use glass vial. This vial contains a total of 0.90 mg of CCH. The manufacturer recommends using a 0.58 mg dose of CCH (Hurst et al. 2009).

21.3.1.1 Mixing

After examining the patient and confirming that CCH is appropriate to use, the CCH must be removed from refrigeration storage and allowed to warm up for 15 min. Remove the diluent from the packaging box to aid in the warm-up. A 1 ml hubless syringe with 0.01 ml graduations and a permanently fixed 27-gauge, 13-mm (1/2-in) needle is used. Do not use a standard Luer-Lok syringe. Back pressure, which commonly occurs during injection, may cause the needle to come off and the CCH may be lost. Check the vial containing the lyophilized powder of collagenase and confirm that the white cake of CCH is present. Inject the

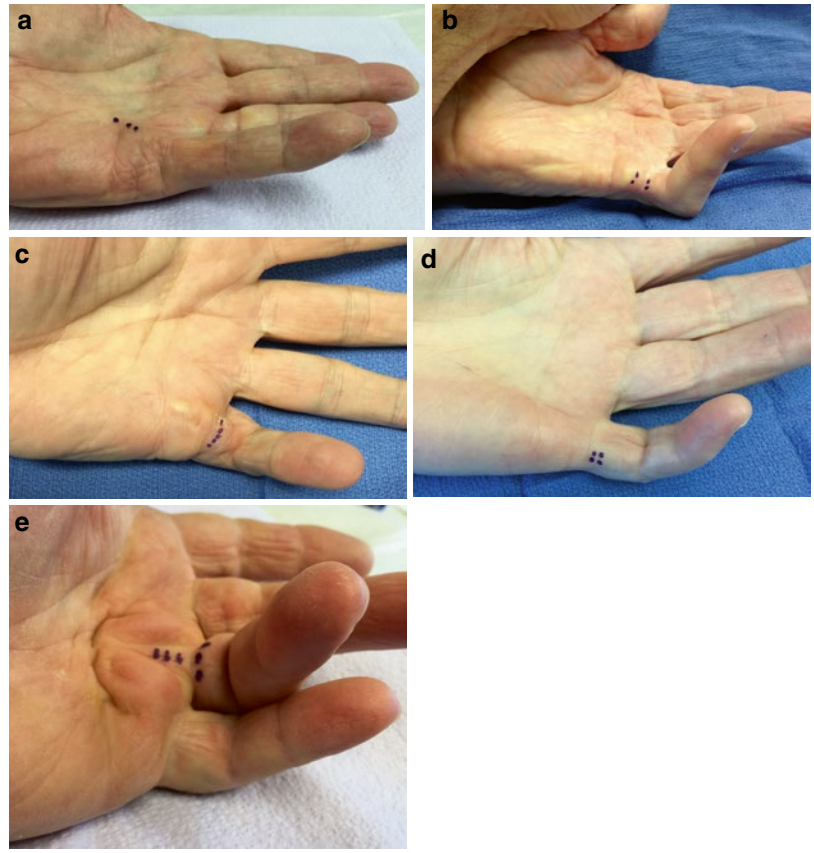

Fig. 21.5 Portal sites for CCH injection. (**a**) Palm × 3 (**b**) proximal to PFC × 2, distal to PFC × 2 (**c**) transverse distal to PFC × 4 (**d**) Box distal to PFC x 4 (**e**) T-shaped – proximal to PFC × 3 and distal to PFC × 3

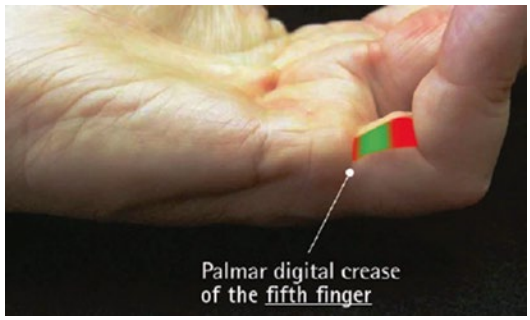

Fig. 21.6 Safe zone for injection distal to the PFC (Courtesy of F. Thomas Kaplan, MD)

diluent slowly into the sides of the vial. For treatment of an MP joint contracture, 0.39 ml of diluent is used. For treatment of a PIP joint contracture, 0.31 ml of diluent is used. Do not shake the vial, but gently swirl to mix the solution.

A fresh syringe can be used for the injection. Pull back the stopper, filling the syringe with air. Rotate the CCH bottle so the stopper notch is facing you. Insert the needle vertically into the vial, which is held upside down. Inject 0.5 cc or more of air into CCH vial and then withdraw the needle, close to entrance point. Rotate the needle so that the bevel is seen within the notch. Hold the bottle and needle vertically so gravity assists in the withdrawal of CCH. If you cannot withdraw the CCH, push the air back into the bottle, then gently rotate the bottle and try withdrawing again. Avoid withdrawing air bubbles into syringe, since the viscosity makes it difficult to tap the bubbles out (Meals and Hentz 2014). Confirm that CCH has been withdrawn from the vial and that the syringe is not just filled with air. For treatment of an MP joint contracture, 0.25 ml of CCH is removed. For treatment of a PIP joint contracture, 0.20 ml of CCH is removed.

21.3.1.2 Injection

Make sure all jewelry and rings are removed prior to injection. Local anesthesia can be

utilized, if desired. Xylocaine 1 % plain is preferred. A wrist block, palmar block, and/or digital nerve block can help minimize the pain associated with the injection. It is advised to avoid placing any local anesthetic directly in the area of the cord that you are injecting. Fluid in the area may make it difficult or even impossible to palpate the cord and accurately inject CCH.

The patient's hand is prepped with antiseptic solution. The cord is bowstringed by extending the finger and applying tension to the cord. Injections are performed at areas of maximum bowstring, since this is the farthest distance from the flexor tendons and neurovascular bundles. Injections should not be placed in flexion creases. Injecting through supple skin is preferred and areas where the skin is adhered to the cord should be avoided. When injecting distal to the proximal finger crease, especially for the little finger, make sure the injection is performed in the safe zone, within 4 mm of the proximal finger crease and no more than 2–3 mm deep. It is not necessary to insert the needle vertically. Inject obliquely, angling the needle away from the underlying flexor tendons. Ulnar cords of the little finger can even be injected transversely in an ulnar to radial direction. Use a "pinch and poke" technique, always feeling the cord when injecting. When injecting, some resistance should be felt. If there is no resistance, remove and readjust the needle. While injecting, if the initial resistance stops, the needle may have penetrated dorsally. Immediately stop injecting, remove the needle from the cord, and reinsert in a different area. If you just withdraw back and continue injecting, you may inadvertently inject dorsally through the cord into the flexor tendon sheath (Fig. 21.7).

The dose is divided into multiple aliquots, spaced 2–3 mm apart. Use a minimum of 4–6 aliquots. The needle can be readjusted under the skin or, preferably, completely removed and reinserted for each aliquot. Injection sites can be aligned longitudinally, transversely (especial for wide cords) or T-shaped around the proximal finger crease. The three-dimensional anatomy of the cord should be kept in mind at all times. The cords are usually very superficial, less than 4 mm beneath the skin. The syringe barrel needs to be stabilized by leaning on the hand, when pushing the plunger. Do not push the needle in deeper when pushing the plunger. The distance between hub of the needle and the skin should be watched closely at all times.

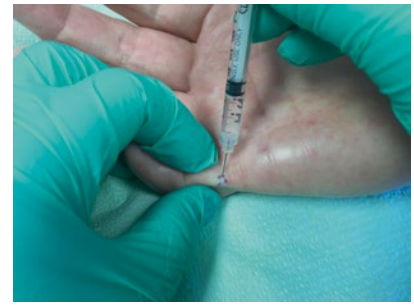

Fig. 21.7 Pinch and poke technique for CCH injection with needle angled away from flexor tendons

The hand is placed in a light dressing, and the patient is asked to avoid any vigorous activity with the hand. Elevation of the hand is recommended, and analgesics may be necessary to control postinjection pain. All patients are educated to expect common side effects. Postinjection and post-manipulation written instructions are provided. Self-manipulation is discouraged.

21.3.2 Manipulation/Finger Extension Procedure

The manipulation/finger extension procedure can be performed 24, 48, or 72 h after injection. Local anesthesia is strongly recommended with lidocaine 1 % plain, lidocaine 2 % plain, or 1 % lidocaine with 1:100,000 epinephrine. Sodium bicarbonate 8.4 % can be used for buffering. Wrist block, palmar block, digital block, ring block, and dorsal block can help minimize the pain associated with the manipulation. Don't hold back on the anesthesia and allow for ample time for the anesthesia to work before manipulating! Light monitored anesthesia care (MAC) in a hospital or surgery center can be used for patients with no tolerance for any pain.

A stack of folded towels is placed under the hand to aid in extension of the MP and PIP joints. The patient's hand is prepped with antiseptic

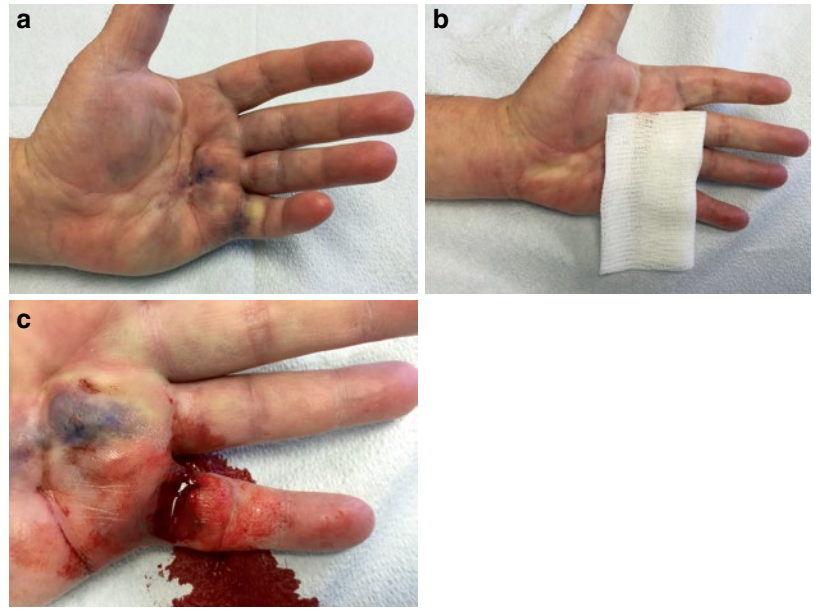

Fig. 21.8 Post-CCH injection (**a**) post-CCH injection swelling, (**b**) gauze covering potential skin tear before manipulation, (**c**) skin tear

solution and gloves are recommended. Areas with a hematoma, blood blister, or tight skin are potential skin tear sites. Skin tears usually occur just distal to the proximal finger crease or just proximal to the middle finger crease. All areas of potential skin tear are covered with a gauze pad to prevent splatter of blood (Fig. 21.8).

The forearm is supinated. Before manipulating the finger, the flexor tendons are protected by flexing the wrist. Manipulate the MP joint first, by flexing the PIP joint extending the MP joint. If there is also a PIP joint contracture, the MP joint is flexed, while the PIP joint is extended. Then the entire finger is extended. A palpable or audible popping of the injected Dupuytren cord may be noted.

The finger is then manipulated in abduction, adduction, pronation, and supination to release all cords. Massage and compress each released cord to help disrupt remaining deep fibers. Manipulating unaffected adjacent fingers one at a time can also help disrupt remaining cords. Immediately after cord rupture, the patient is asked to flex and extend their fingers to confirm tendon integrity.

If the manipulation attempt fails, wait 10–15 min and try again. If significant contracture remains, the patient can return 30 days later for a repeat injection of CCH, or PNF can be attempted. PNF can be difficult to perform immediately after a failed manipulation, due to ecchymosis and edema.

If a skin tear occurs, pressure and elevation is used to control bleeding, and standard local wound care with dressing changes is utilized. A splint is fitted immediately post-manipulation, and night use is recommended for three to four months. Patients are instructed to exercise at home 5–10 min twice a day for 4 weeks. Written instructions are provided, including specific active range of motion exercises in flexion, extension, abduction and adduction, and gentle passive stretching. It is recommended that patients avoid heavy grasping for the first 2 weeks. Therapy is not needed in most instances. Hand therapy with splinting can be ordered for residual contractures and to treat PIP joints that have regained full passive extension, but have a residual active extension lag (central slip laxity) (Skirven et al. 2013).

21.3.3 Tips and Pearls

Author's Tips and Pearls

Collagenase/Xiaflex/Xiapex

Carefully explain common side effects before injection.

Use anesthesia for the injection and especially for the manipulation.

Maintain tension on cord during injection.

Choose areas of maximum bowstring for injection.

Inject cords utilizing the safest angle.

Inject wide cords transversely.

Remember the safe zone.

Divide injection into more than 3 aliquots.

Manipulate after 24 h.

Prep first and cover any potential skin tear sites with a gauze pad before manipulating.

Manipulate finger into extension, adduction, adduction, pronation, and supination.

Manipulate adjacent fingers into extension.

Conclusion

There is no cure for Dupuytren contracture. No matter what procedure is chosen, the disease may recur. Until a genetic or disease-modifying treatment can be found, minimally invasive treatments should be considered. These techniques offer a combination of excellent efficacy, significant improvement of range of motion, low complication rate, and quick recovery (Figs. 21.9 and 21.10).

Conflict of Interest

Royalties/honoraria received from Biomet
Speakers bureau with Auxilium
Contracted research: Auxilium

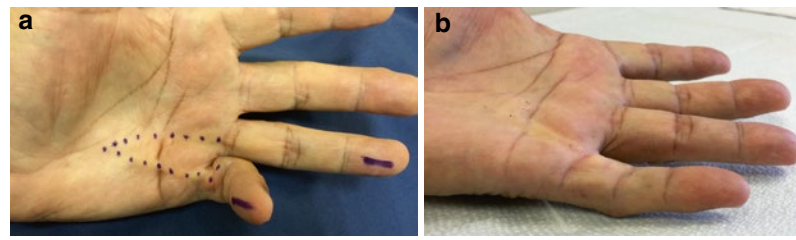

Fig. 21.9 Successful treatment with PNF (**a**) pre (**b**) post

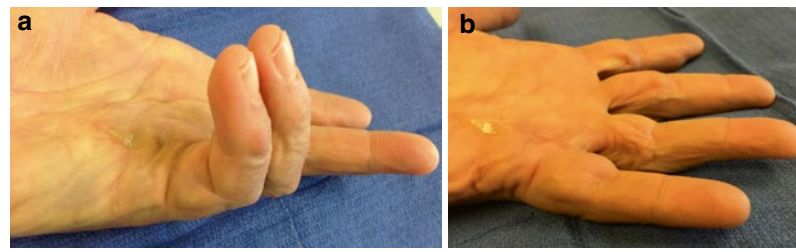

Fig. 21.10 Successful treatment with CCH (**a**) pre (**b**) post

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22 Clinical Results of Percutaneous Needle Fasciotomy for Dupuytren Contracture: Are There Significant Correlations Between Preoperative Dupuytren Diathesis Score and Contracture Recurrence?

Yoshihiro Abe

Contents

22.1 Introduction

Percutaneous needle fasciotomy (PNF) is an alternative treatment for Dupuytren contracture (DC). PNF has the advantage of being a faster and less invasive procedure and can even be performed in an outpatient setting using local anesthesia. However, it tends to result in greater recurrence rates (Foucher et al. 2003; van Rijssen and Werker 2012; van Rijssen et al. 2012) under these circumstances. Recurrence rates are an important consideration when evaluating the effectiveness of treatment for DC. Prognostic factors for recurrence have previously emphasized clinical features identified with more aggressive disease, such as younger age of onset, strong family history, distant disease (e.g., Peyronie and Ledderhose Disease), and bilaterality following limited fasciectomy or dermofasciectomy (Hueston 1984). There are few quality studies that have assessed factors that can influence the risk for recurrence following PNF. This study focuses on the relationship between recurrence rates and Abe's diathesis score at three-year intervals following PNF (Abe et al. 2004b). This score was calculated as follows: $D = a + b + c + d + e + f$, where D = the diathesis score, a = bilateral hand involvement (with = 1, without = 0), b = little finger surgery (with = 1, without = 0), c = early onset of disease (with = 1, without = 0), d = plantar fibrosis (with = 2, without = 0), e = presence of knuckle pads (with = 2, without = 0), and f = radial side involvement (with = 2, without = 0). Our definition of the radial

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side involvement was disease affecting the thumb, first web space, and the radial aspect of the index finger (Abe et al. 2004a).

22.2 Materials and Methods

22.2.1 Study Design

This prospective study was designed and approved by the local Medical Ethics Committee in September 2011. From October 2011 to June 2014, every patient with DC who could be followed for more than one year was assessed for enrollment in the study. Written consent was obtained from all patients at study entry. Seventy-seven patients were consecutively enrolled in this study. PNF was offered to all those patients with DC who had a clearly defined pathologic cord with a flexion contracture of at least 30° when measured using the total passive extension deficit (TPED) and who were willing to participate in the study. At initial presentation, the flexion contractures of the metacarpophalangeal (MCP) joints and the proximal interphalangeal (PIP) joints of the involved finger rays were measured. Patients were divided into 2 groups, one with a diathesis score >4 patients ($D>4$ group) and the other with a diathesis score ≤4 patients ($D\leq 4$ group).

Recurrence was defined as an increase in the PED of at least 20° compared with the value documented at 6 weeks in each joint and digital ray (Fig. 22.1). Patients were assessed postoperatively after 1 day, at 1, 2, 4, 6, and 8 weeks, at 3, 6, and 9 months, and at 1, 2, and 3 years.

22.2.2 Operative Technique

All affected rays of a hand were treated during a single session. Portal sites in areas of definite cords were carefully chosen and marked with a surgical marker. Portals were spaced 5 mm apart and were not made in skin creases. After marking the portals, 0.1 mL or less of a lidocaine 1 % w/v solution and epinephrine (1:100,000) were injected into each site to be treated. Working in a distal-to-proximal direction, a 25-gauge needle was used as a scalpel to release the cord at multiple levels. As previously described by Eaton (2011), three basic moves—clear, perforate, and sweep—were performed to transect diseased cords. The needle was changed frequently to maintain sharpness. After division of the cord, the fingers of treated rays were passively extended to obtain maximal release. Portals and nodules were subsequently injected with a 10 mL lidocaine 1 % w/v solution and 20 mg triamcinolone acetate mixture because its efficacy had been proved by McMillan and Binhammer (2012) in their randomized controlled trial study, and it is also known that steroids downregulate cell proliferation and induce apoptosis by affecting collagen ratios and fibroblast activity at the molecular level (Meek et al. 1999, 2002).

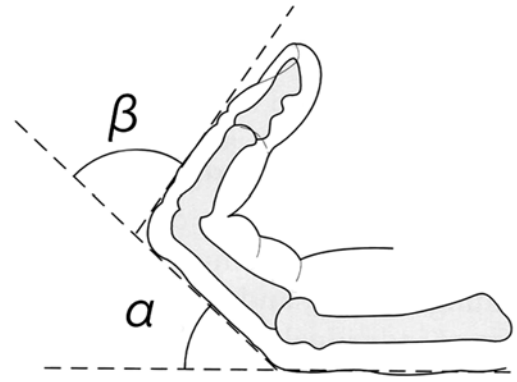

Fig. 22.1 Assessment of flexion deformity for rays and independent joint. α PED of MCP joint, β PED of PIP joint, $\alpha+\beta$ TPED of ray. *TPED* the total passive extension deficit, *PED* the passive extension deficit

Postoperatively, a light gauze bandage dressing was applied and removed the next day if the skin had not ruptured. Immediately after the procedure, a fiberglass volar or ulnar gutter splint was applied to mold night splint, and its use at night was recommended for up to 3 months. No restrictions were applied to daily activities. Patients were encouraged to start increasing the motion of their hand immediately after the procedure, although they did not receive formal hand therapy.

22.2.3 Statistical Analysis

Fisher's exact test was used to determine the association between categorical variables. A significance level of $p < 0.05$ was used.

22.3 Results

Initially 77 patients were included. Of these 77 patients, 2 patients were lost to follow-up due to other medical problems or death, 3 patients dropped out because they wanted to undergo limited fasciectomy, and 5 patients moved far away from authors' institute. Therefore, this case series consisted of 67 patients (59 men and 8 women) with 123 fingers and involved 112 MCP joints and 84 PIP joints. The average age at surgery was 66.8 ± 6.8 years. The patient profile and characteristics of our case series are shown in Table 22.1.

Based on their Abe's score at the time of entry to this study, 50 patients were allocated to the D ≤4 group and 17 patients were allocated to the D >4 group. A total of 52 right hands and 46 left hands required PNF and 3 index, 13 middle, 52 ring, and 55 small finger rays underwent PNF.

Depending on the parameter used (patients, hands, MCP, PIP), recurrence rates were 18.8–44.0 % at the 1-year follow-up (Table 22.2), 33.8–53.8 % at the 2-year follow-up (Table 22.3), and 41.5–65.2 % at the 3-year follow-up (Table 22.4). The recurrence rate *p*-values and odds ratios, pertaining to each parameter assessed for both cohorts at each year of the 3-year follow-up, are summarized in Tables 22.2, 22.3, and 22.4, and longitudinal data of each parameter was shown in Fig. 22.2. Of note, the odds ratio for recurrence was significant for digital rays and MCP joints at the 2- and 3-year follow-ups in the D >4 group (Fig. 22.3). However, there were no statistically significant differences in the recurrence rates between the D >4 group and the D ≤4 group in patients, hands, and PIP joints at yearly intervals over the 3 years of follow-up.

Table 22.1 Patient characteristics at each follow-up

D>4	Time of postoperative follow-up		
Characteristic	1 year	2 years	3 years
Patients, *n*	17	9	4
Mean age, years ± SD	60.8 ± 11.2	59.7 ± 15.2	58.9 ± 15.8
Male/female, *n*	17/0	9/0	4/0
Diabetes, *n* (%)	4 (24 %)	4 (44 %)	2 (50 %)
Current alcohol use, n (%)	0 (0 %)	0 (0 %)	0 (0 %)
Family history of Dupuytren contracture [DC], *n* (%)	2 (12 %)	2 (22 %)	1 (25 %)
Knuckle pads *n* (%)	10 (58 %)	4 (44 %)	2 (50 %)
Ledderhose Disease, *n* (%)	5 (29 %)	3 (33 %)	2 (50 %)
DC onset age <45 years, *n* (%)	3 (18 %)	3 (33 %)	1 (25 %)
Site of DC, *n* (%)			
Radial side	7 (41 %)	5 (56 %)	4 (100 %)
Little finger	16 (94 %)	8 (89 %)	4 (100 %)
Bilateral	14 (82 %)	7 (78 %)	4 (100 %)
D≤4			
Characteristic	1 year	2 years	3 years
Patients, *n*	50	40	19
Mean age, years ± SD	68.8 ± 8.8	67.1 ± 7.2	72.2 ± 6.2
Male/female, *n*	42/8	36/4	17/2
Diabetes, *n* (%)	12 (24 %)	5 (13 %)	2 (12 %)
Current alcohol use, *n* (%)	2 (4 %)	1 (3 %)	0 (0 %)
Family history of Dupuytren contracture [DC], *n* (%)	0 (0 %)	0 (0 %)	0 (0 %)
Knuckle pads *n* (%)	2 (4 %)	1 (3 %)	1 (5 %)
Ledderhose Disease, *n* (%)	2 (4 %)	1 (3 %)	1 (5 %)
DC onset age <45 years, *n* (%)	0 (0 %)	0 (0 %)	0 (0 %)
Site of DC, *n* (%)			
Radial side	3 (6 %)	2 (5 %)	1 (5 %)
Little finger	25 (50 %)	24 (60 %)	9 (47 %)
Bilateral	40 (80 %)	33 (83 %)	14 (74 %)

Table 22.2 Dupuytren contracture recurrence rate at the 1-year follow-up

	Patients ($n=67$)	Hands ($n=99$)	MCP joints ($n=112$)	PIP joints ($n=84$)
Overall, % (n)	35.8 (24/67)	35.6 (35/99)	18.8 (21/112)	44.0 (37/84)
$D>4$, % (n)	47.1 (8/17)	41.7 10/24	32.1 (9/28)	50.0 (13/26)
$D\leq4$, % (n)	32.0 (16/50)	33.3 (25/75)	14.3 (12/84)	41.7 (24/58)
P-values ($D>4$ vs. $D\leq4$)	0.3801	0.4716	0.0500	0.4854
Odds ratio (95 % CI)	1.89 (0.61, 5.80)	1.43 0.56, 3.67	2.84[a] (1.04, 7.74)	1.42 (0.56, 3.59)

CI confidence interval, *D* diathesis score, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal
[a]Statistically significant

Table 22.3 Dupuytren contracture recurrence rate at the 2-year follow-up

	Patients ($n=49$)	Hands ($n=63$)	MCP joints ($n=66$)	PIP joints ($n=52$)
Overall, % (n)	38.8 (19/49)	41.3 (26/63)	39.4 (26/66)	53.8 (28/52)
$D>4$, % (n)	55.6 (5/9)	66.7 (8/12)	73.3 (11/15)	71.4 (10/14)
$D\leq4$, % (n)	30.0 (16/40)	35.3 (18/51)	29.4 (15/51)	47.4 (18/38)
P-values ($D>4$ vs. $D\leq4$)	0.4698	0.0582	0.0015	0.2093
Odds ratio (95 % CI)	1.88 (0.44, 1 8.0)	3.67 (0.97, 13.87)	8.80[a] (2.69, ∞)	2.78 (0.74, 10.43)

CI confidence interval, *D* diathesis score, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal
[a]Statistically significant

Table 22.4 Dupuytren contracture recurrence rate at the 3-year follow-up

	Patients ($n=23$)	Hands ($n=34$)	MCP joints ($n=36$)	PIP joints ($n=23$)
Overall, % (n)	56.5 (13/23)	50.0 (14/34)	47.2 (17/36)	65.2 (15/23)
$D>4$, % (n)	100 (4/4)	62.5 (5/8)	85.7 (6/7)	75.0 (6/8)
$D\leq4$, % (n)	47.4 (9/19)	31.0 (9/29)	37.9 (11/29)	60.0 (9/15)
P-values ($D>4$ vs. $D\leq4$)	0.1045	0.2152	0.0365	0.6570
Odds ratio (95 % CI)	9.95 (0.47, 210)	3.70 (0.72, 18.97)	9.82[a] (1.04, 92.78)	2.00 (0.30, 13.44)

CI confidence interval, *D* diathesis score, *MCP* metacarpophalangeal, *PIP* proximal interphalangeal
[a]Statistically significant

22.4 Discussion

Recurrence is relatively common in patients treated for DC, and the rational selection of therapy depends on understanding the risk for this outcome with different interventions. When assessing recurrence of DC, there are two main problems: (1) definitions used to describe recurrence have been highly variable, vague, or nonexistent and (2) follow-up durations can be varied or misaligned. Elsewhere, in a systematic review of the literature (Becker and Davis 2010), recurrence rates following surgery were estimated to range from 0 to 71 % in studies with follow-up periods of between 3 weeks and 13 years; however, the authors highlighted that there was significant variation in how recurrence rates were measured and reported. They concluded that the outcome of surgery was inconsistent and that this inconsistency may have been related to the different definitions used for recurrence.

A number of definitions can be found in the literature for recurrence (Abe and Tokunaga 2015; Badalamente and Hurst 2007; Leclercq 2000; Pereira et al. 2012; Pess et al. 2012; van Rijssen et al. 2006; Watt et al. 2010). In PNF studies, recur-

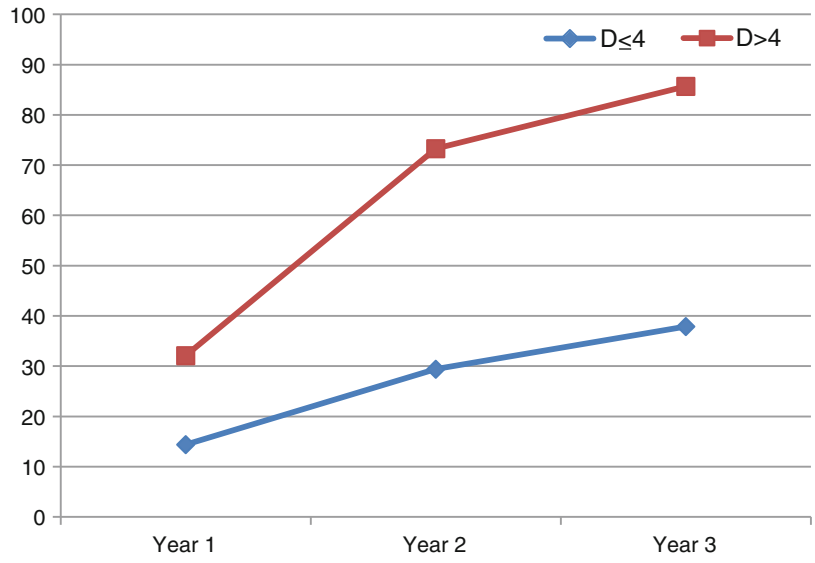

Fig. 22.2 Diathesis score versus MCP recurrence rate. Longitudinal data for the recurrence rate on the MCP joint each 3-year follow-up. Recurrence rates were statistically significantly higher in $D>4$ patients

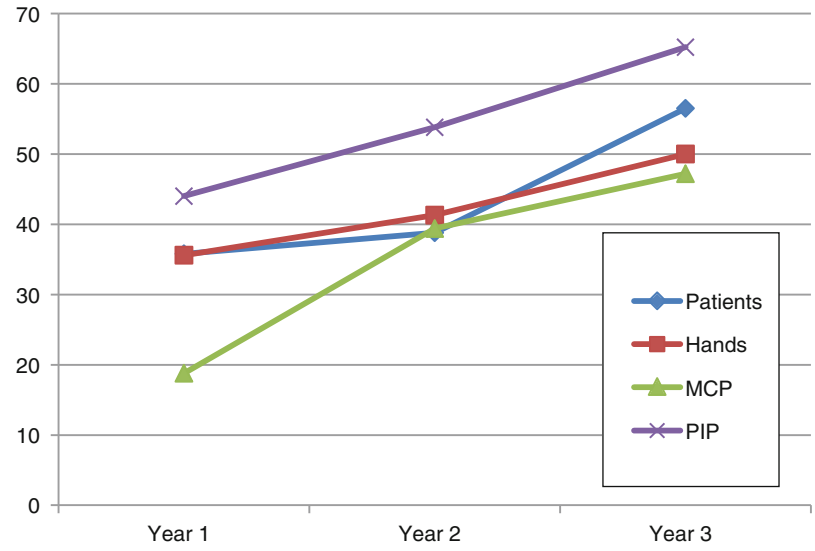

Fig. 22.3 Recurrence rate versus recurrence parameter

rence has been defined differently, as a 20–30° increase in TPED (Abe and Tokunaga 2015; van Rijssen et al. 2006), 20° increase in PED (Abe and Tokunaga 2015; Pess et al. 2012), as recurrent joint contracture sufficient to require further surgery (Pereira et al. 2012), or as the need for retreatment (Duthie and Chesney 1997). Moreover, denominators were also varied based on the number of patients, affected hands, digital rays, and/or joints involved. Follow-up periods have varied from 6 weeks up to 5 years. Therefore, reported recurrence rates vary in range from 9 to 85% for PNF (Abe and Tokunaga 2015; Badois et al. 1993; Duthie and Chesney 1997; Foucher et al. 2003; Pereira et al. 2012; Pess et al. 2012; van Rijssen et al. 2006, 2012; van Rijssen and Werker 2012).

Recurrence rates are highly dependent on the time between treatment and the follow-up

examination. It is commonly accepted that recurrence rates increase in proportion to follow-up duration (Beaudreuil et al. 2011; Pess et al. 2012; Jurisić et al. 2008; Dickie and Hughes 1967; Norrote et al. 1988; Watt et al. 2010). In long-term follow-up studies, remarkably high recurrence rates of 63.6 % at 3 years and 84.9 % at 5 years have been reported following PNF (van Rijssen and Werker 2012; van Rijssen et al. 2012). It has also been reported that the diathesis score, or each component of it, did not correlate with recurrence, and only the age at surgery has been a statistically significant factor. In contrast, in the present series, Abe's diathesis score did not predict recurrence for patients, hands, and the PIP joints treated with PNF. However, it might be a better predictor of recurrence for digital rays and the MCP joints that have been treated with PNF at least 2-years post PNF. The reason for this discrepancy would likely arise from the fact that van Rijssen and colleagues (2012; van Rijssen et al. 2012b) calculated recurrence rate only per hand, using that as a denominator. Our previous study revealed several clinical results of PNF; the recurrence rate can be represented in various ways using different denominators that can result in outcomes varying by as much as 22–39 % in the same sample (Abe and Tokunaga 2015. The effect of the Abe diathesis score may be most obvious in MCP joints because the baseline MCP recurrence rate after PNF is low compared to PIP recurrence. The high rate of PIP recurrence after PNF may have overshadowed the effect of the Abe diathesis score. When comparing our 3-year results to those of the Rijssen and Werker (2012a) series, overall recurrence rates per hand were relatively lower in our series (50.0 % vs. 63.6 %). This discrepancy can be attributed to the different definitions for recurrence used. We use an increase of 20° in the PED for each joint, respectively, while van Rijssen et al. (2012b) used 30° in the TPED. Furthermore, the local injection of triamcinolone acetate might also be an influential factor attenuating recurrence in our series (McMillan and Binhammer 2012). There would likely be racial differences between white and Asian patient cohorts. Werker et al. (2012) concluded that clearly defined objective definitions for the correction of contractures and for recurrences are needed for more meaningful comparisons of results achieved with different surgical interventions. It is the authors' opinion that recurrence should be evaluated annually because different follow-up durations make it impossible to meaningfully compare recurrence results, even within the same intervention. Therefore, our approach of performing annual follow-up evaluations out to 3 years in the present study seems to be a reasonable way to address this concern.

There were several limitations of this study. The number of patients that could be followed up for the 3 years was relatively small. Also, the 3-year follow-up may be too short a time period in which to accurately determine the actual recurrence rate, which may change over an extended period of time. Recurrence rates are highly dependent on the time between treatment and the follow-up examination. Based on this, it is important to standardize follow-up periods to avoid discrepant durations which can bias results related to recurrence. Standardizing the reporting of results will allow for more meaningful comparisons of different treatments for DC in the future. Also, the meanings of DC correction and of recurrence were clearly defined for patients in this study, and an annual follow-up was provided out to 3 years.

Conclusions

- Diathesis scores had disease recurrence prediction value at least 2 years after PNF for digital rays and MCP joints.
- Diathesis scores may not predict disease recurrence in patients, hands, and PIP joints following PNF.

Conflict of Interest Declaration The author has no conflict of interest to declare.

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23 Effectiveness of Percutaneous Needle Fasciotomy for Second or Higher Recurrence in Dupuytren Contracture

Margot A. Vlot and Paul M.N. Werker

Contents

23.1 Introduction

Patients suffering from Dupuytren Disease (DD) have many different options for treatment, with different outcomes regarding short-term improvement, recurrence rates and invasiveness of the treatment. The standard treatment is limited fasciectomy (LF). For most physicians, LF has the best balance between recurrence, cost, invasiveness and improvement of total passive extension deficit (TPED). Nevertheless, many patients prefer a treatment with percutaneous needle fasciotomy (PNF), due to its less invasive character and short recovery (Henry 2014). PNF has been shown to be an effective treatment for first contractures and first recurrences in DD (Pess et al. 2012; van Rijssen et al. 2012; van Rijssen and Werker 2012). Reported recurrence rates vary from 50 to 85 % at 5-year follow-up after PNF (van Rijssen and Werker 2012). The reason these figures vary so greatly is the lack of standard definitions for recurrence. The role of PNF is controversial because of high recurrence rates (Werker 2016). What remains unclear is whether or not PNF is a viable option for treatment of second or higher recurrences of DD. If so, it could mean that several treatments with PNF could be comparable to LF. Therefore, our research question is: 'Is PNF an effective treatment option for second, third and fourth recurrences of DD?'

23.2 Material and Methods

A retrospective medical file study was conducted on patients treated for recurrent DD in the University Medical Center Groningen between 2007 and 2014, regardless of where and how they were treated for their first contracture. Patients were identified using operation codes for

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PNF. Inclusion criterion for this study was the third, fourth or fifth treatment of the same ray. The primary outcome measurement was the reduction of TPED as a result of third, fourth or fifth treatment. The time to subsequent recurrence was also recorded, as was the time of the first visit to the clinic to the treatment with PNF. The choice of treatment, LF or PNF, was always made by the patient.

Data were collected in Microsoft Excel 2010. The unpaired *t*-test was used to determine if the reduction of TPED as the result of third, fourth or fifth PNF was statistically significant ($p < 0.05$).

23.3 Results

One hundred and seventy-two rays were treated with PNF for a first contracture. Four rays had LF for the first contracture. Fifty-seven rays were seen with a first recurrence. Thirty-nine rays were treated with another PNF. Sixteen rays were seen with a recurrence after a second PNF. We found that 11 rays (11 patients) underwent PNF for a second recurrence, 4 rays (4 patients) for a third recurrence and 3 rays (2 patients, 3 hands) for a fourth recurrence. All recurrences seen in the UMCG were treated by the same physician. In every group, there were several patients who received treatment elsewhere prior to coming to the UMCG for treatment on their recurring contracture. Mean TPED reduction after a third, fourth and fifth treatment was, respectively, 73 %, 63 % and 27 %. Results showed a trend towards less effective treatment at PIP level than at MCP level, irrespective of treatment number (25 % more reduction of PED at MCP level after second and third PNF than at PIP). A case that was treated three times with PNF is illustrated in Fig. 23.1. An overview of the number of patients treated is shown in Fig. 23.2, whereas Fig. 23.3 shows an overview on the reduction of TPED. There were zero complications documented after PNF treatment in the medical files. By means of PNF, a more aggressive treatment was postponed in this selected subset of cases with an overall average of 4.5 years.

Shown are the numbers of rays treated for primary DD or recurrences. The number of rays that were treated with PNF are shown, as well as the numbers of rays that were treated with LF. The patients who chose LF at any moment were not further included in the study. There was one ray included that had PNF for the first contracture, LF for the first recurrence and PNF for the second recurrence.

A third and fourth treatment with PNF were equally as effective as a primary or second treatment ($p = 0.738$).

23.4 Discussion

The aim of this study was to find out if PNF is an effective treatment option for second or higher recurrences of DD. This study showed that the effectiveness of PNF for second and third recurrences was high. Even with a fourth treatment with PNF, we found similar results as with primary PNF results described in literature (van Rijssen et al. 2012; van Rijssen and Werker 2012). Unfortunately, a fifth treatment was not as effective as earlier treatments, although the number of cases is small.

23.4.1 Strengths of the Study

As far as we know, there has not been any research published on the effectiveness of PNF for second of higher recurrence in DD. This study, being the first of its kind, is therefore an important first step. Furthermore, the largest possible group of patients was included for this study by including all patients treated from 2007, when the procedure was first performed in our hospital, until 2014.

23.4.2 Weaknesses of the Study

In spite of including as many patients as possible in our hospital, the patient groups that underwent multiple treatments with PNF are small. Since recurrence of DD is unpredictable and can occur

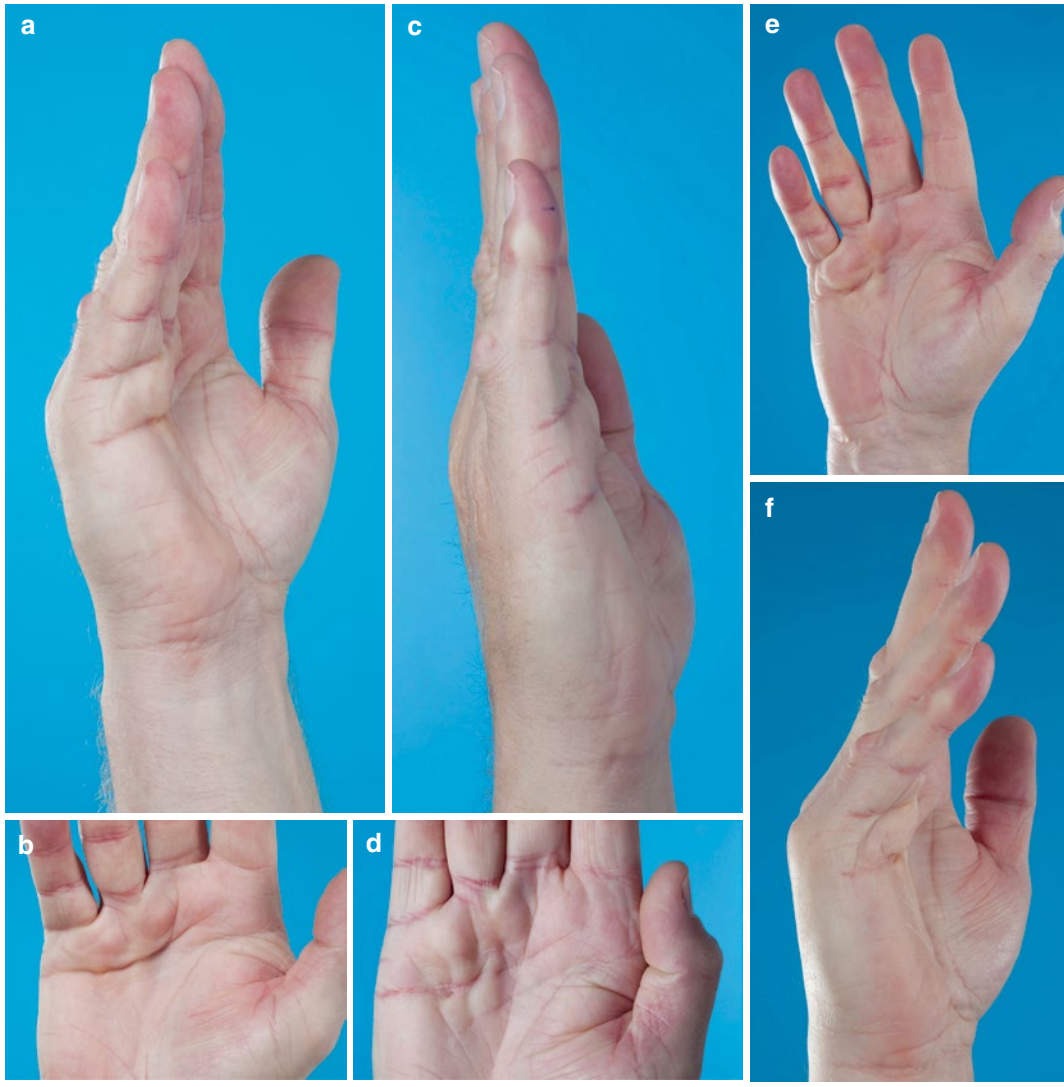

Fig. 23.1 59-year-old male, who had his first PNF at the age of 54 for right middle, ring and small MCP contractures (**a**, **b**, before the first PNF; **c**, **d**, 1 year after the first PNF). Two years after the first PNF, he developed a recurrence in his right hand (**e**, **f**), which was treated again with PNF because of a 50° small MCP contracture and a 35° ring MCP contracture. The contractures were corrected completely (**g**, **h**). Three years after his second PNF, his right hand was treated again for a 30° small MCP contracture and a 60° small PIP contracture (**i**, **j**). These contractures were corrected to 0° and 20°, respectively (**k**, **l**)

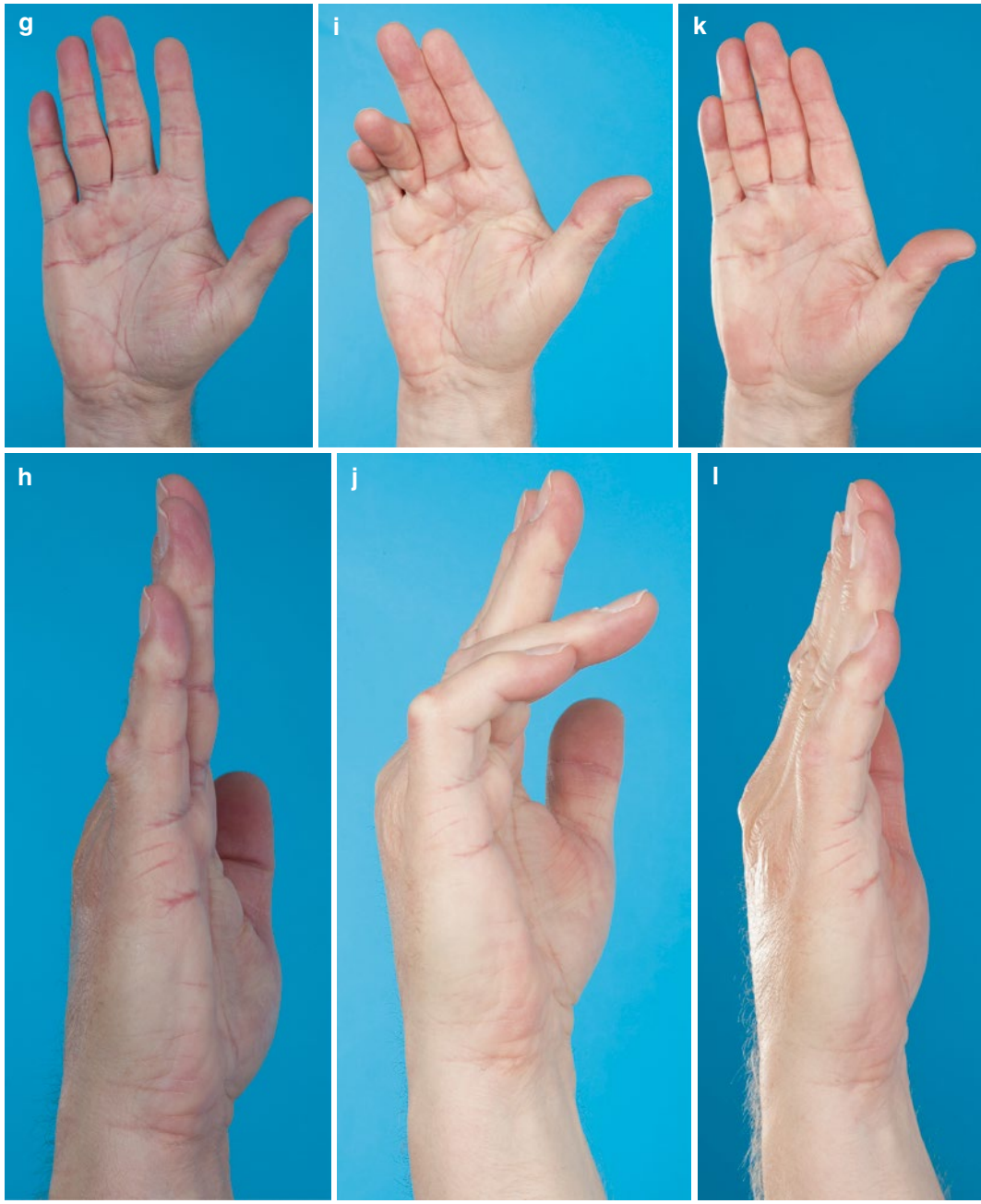

Fig. 23.1 (continued)

after many years, this problem can only be solved by including more patients over a larger time span. The status of patients that did not return for treatment is not known, so these patients were lost to follow-up. Therefore, clear figures on recurrence after repeated PNF cannot be stated. Moreover, due to the retrospective nature of this study, the quality of the data was poor and reduction of TPED was often not recorded postoperatively. This also explains the difference in group

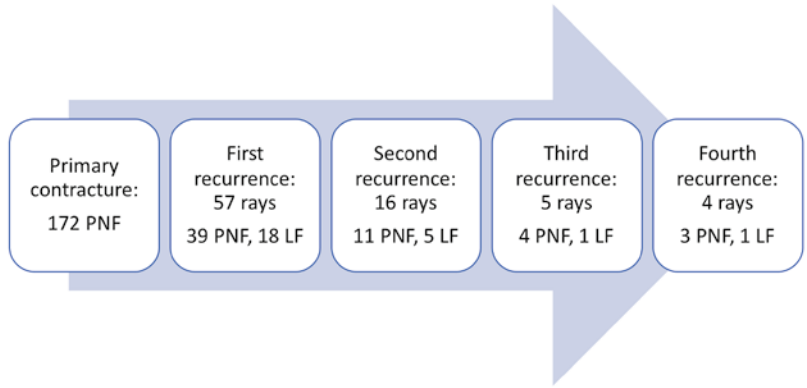

Fig. 23.2 Overview of rays treated by PNF in between 2007 and 2014

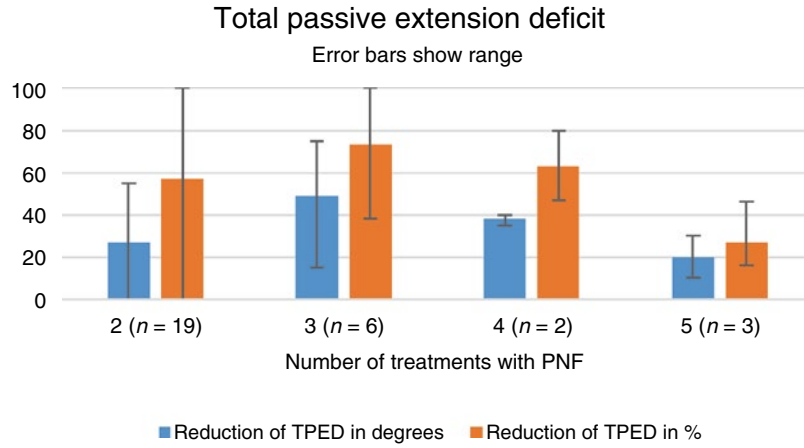

Fig. 23.3 Overview of reduction of TPED

size presented in Figs. 23.2 and 23.3. The patients included in this study have made their own informed decision on which treatment they wanted to undergo for their contracture. In 2007, not much was known about the success of repeated PNF. Now that we have an indication that repeated PNF is a viable option for treatment, physicians are able to inform their patients better and therefore have more patients choose PNF over LF for their recurred contracture. The lack of knowledge might have influenced the decisions of our included patients in a negative manner.

23.4.3 On Time to Recurrence

Because a total of twenty-five rays included in the study had their primary treatment with PNF elsewhere, the time to recurrence could not be measured accurately. We did measure the time from the patient's first visit to the clinic to the moment of more invasive surgery or, if there was no LF registered, to the end date of the entire study. In this way, we can say that a more aggressive treatment was postponed on average with 4.5 years. This result shows that even if PNF is not the best option for all patients suffering from DD, it provides a minimally invasive option that can postpone a more invasive option in a substantial group of cases. Especially for the elderly, in whom recurrences do not occur as rapidly as in the younger age group, this approach is appealing. For younger patients, who prefer a minimally invasive procedure due to work or personal circumstances, (repeated) PNF is a viable option for treatment. If these young patients can be treated properly with

repeated PNF, perhaps in the long run they will never need treatment with LF.

Conclusions

- This study showed that the effectiveness of PNF for second and third recurrences was just as high as of a first treatment with PNF.
- A fifth treatment with PNF was less successful.
- This study gives a useful first insight in the effectiveness of PNF for secondary or higher recurrences in DD. Nevertheless, further research is needed.

Acknowledgements and Conflict of Interest Declaration Photographs shown are reprinted with kind permission from: Werker, PMN and Reichert, B: Percutaneous Needle Fasciotomy. In: Dupuytren Disease, Instructional Course Book, FESSH. Ed: D. Warwick. (2015) Publisher: C.G. Edizioni Medico Scientifiche, Via Piedicavallo 14–10145 Torino

Paul M. N. Werker has participated in advisory board meetings for Pfizer Ltd and Sobi Ltd regarding the use of collagenase for Dupuytren Disease and has been a trainer for Pfizer Ltd in the use of collagenase for DD. Margot A. Vlot has no conflict of interest to declare.

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Controversy: How to Treat Severe PIP Contractures? - Collagenase Treatment

24

Clayton A. Peimer

Contents

24.1 Introduction

Interphalangeal joint (IPJ) contractures from Dupuytren Disease are frequently problematic. They are both more difficult to treat and more challenging to maintain correction than metacarpophalangeal (MPJ) joint deformities (Tubiana 1999). Historically, when surgery was the only available treatment, "successful" outcome generally meant about a 24° *improvement* and which translates as about a 50 % contracture reduction. The prognosis for improvement with open surgical treatment is worsened when the IPJ deformity has been long standing and involves volar capsule, flexor (adherence), and/or extensor (stretching) tendons and when the IPJ deformity is more severe (generally defined as >50°) and in the presence of comorbid diseases (e.g., diabetes mellitus) or risky lifestyles (e.g., cigarette smoking) (Smith 1991; Rayan 2007).

The literature documents that all joint corrections deteriorate with time and that the IPJs are more labile (Peimer et al. 2015a, b). Postoperative studies with longer follow-up show ultimately worsened results as recurrent disease, recurrent contracture, and new disease, plus small joint deterioration in an aging population that generally only presents after about age 50. The need for reoperation therefore increases after three, five, and 10 years, and technical challenges and complications increase for a secondary surgical treatment.

24.2 Drawbacks of Fasciectomy

Open fasciotomy and/or fasciectomy operations may inflict a prolonged or painful recovery. Surgical and postoperative complications are reported in 17–50 % cases (Desai and Hentz 2011; Peimer et al. 2015a, b), including iatrogenic injuries to nerves, vessels, and tendons. Many patients already have preexisting finger joint osteoarthritis and numbers are actually worse/more dysfunctional than preoperatively,

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even excluding iatrogenic problems, because of postoperative arthrofibrosis in the absence of complex regional pain disorder. Hand therapy is necessary after most surgeries and can be disruptive, time consuming, and expensive. Aggressive "radical" fasciectomy, which was advocated early in the twentieth century, progressively fell out of favor for these reasons and has largely been abandoned.

24.3 Needle Fasciotomy: An Alternative?

The advent of percutaneous needle fasciotomy (PNF) (also called "needle aponeurotomy," abbreviated as NA) has offered a less expensive, less invasive, and often more rapid correction. However, the literature corroborates that NA may offer less correction than open surgical treatment. Of additional concern is that longer studies suggest strongly that NA may also offer less durable improvement than open surgery (van Rijssen et al. 2012).

24.4 Advantages of Using CCH

Looking at the reality of recurrence (defined in most studies as ≥30° total passive extension deficit worsening) after open surgery, it has ranged in reports from 5 % at 10 years to 70 % at 7 years. Recurrences after NA have been reported as high as 85 % at 5 years (van Rijssen and Werker 2006; van Rijssen et al. 2012). Recurrences after enzymatic fasciotomy using collagenase *Clostridium histolyticum* (CCH) are now published and are, in aggregate, 46 % 5 years after treatment when using a 20° single joint passive extension deficit threshold for recurrence and 32 % when using a 30° single joint passive extension deficit threshold for recurrence. As with other treatments, interphalangeal joints with more severe deformity do not do as well as those with less initial contracture (Peimer et al. 2015a, b).

Residual and/or recurrent disease, skin and tendon scarring, capsular contracture, and arthrofibrosis plus joint degeneration in aging patients are wary of having "another operation" and "going through all that" pain, dysfunction, time, and expense again. For these reasons, my own experience has been affirmative in using enzymatic fasciotomy both for primary corrections and for recurrences after both surgery and prior CCH treatment.

24.5 Treating the Real Patient

This is a perfect place to reemphasize that no presently available treatment cures this disease and that recurrences and new disease must be expected in the fullness of time. Patients should be informed of and understand this reality before any treatment commences. The author believes in repeating that truth throughout the longer term after any method of correction.

However, I would also emphasize that for primary disease and recurrences, no one treatment "fits all types" of situations. Some "recurrent deformities" are due to skin cicatrix and joint and tendon fibrosis; some are therefore not suitable for NA or an enzymatic approach that require both deformity and a *causative* fascial cord.

In treating real patients, one must consider the overall disease as with the individual shown in Fig. 24.1, IP joint contracture may be due to a "double digital cord" and that may be accompanied by a palmar fascial cord as well.

Patient #2 is a male in his third decade with a strongly positive family history (Fig. 24.2).

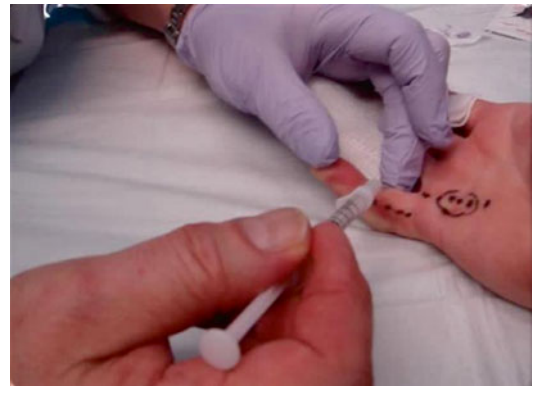

Fig. 24.1 Patient #1, with double digital cord

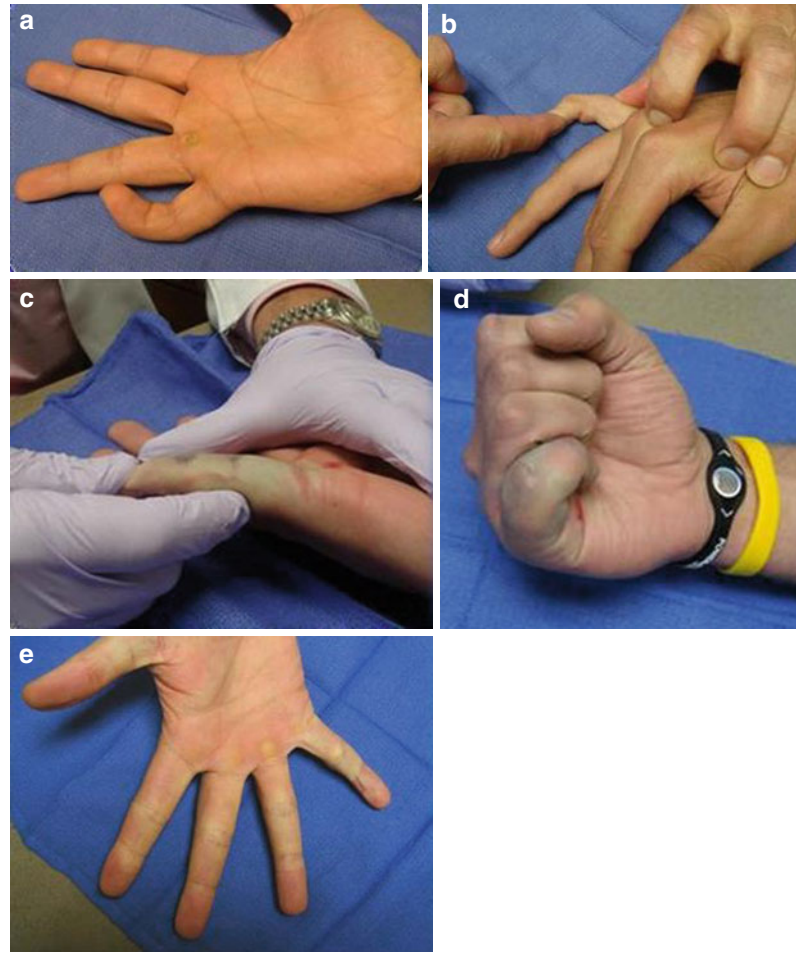

Fig. 24.2 Patient #2, with combined PIP and DIP contracture. We see combined proximal and distal interphalangeal joint contractures in the little finger (**a**, **b**). When injecting the CCH, one aims the needle away from the flexor sheath at all times. Correction is seen in the immediate post-manipulation photographs (**c**, **d**) (the finger is pale after use of anesthetic containing epinephrine). (**e**) Shows the 35-month follow-up with physiologic PIPJ hyperextension

Patient #3 is a gentleman early in his eighth decade who presented for consultation about 4 years after surgery done elsewhere for left little finger PIP contractures. He was referred to our clinic because he said he would "never again" go through an operation, but he was most interested in alternative approach to gaining correction. At the consultation visit, he was given verbal and written education about the nature of the disease and recurrences after any form of treatment. He was actually quite well informed after his surgical experience and subsequent Internet research. He had learned about enzymatic treatment and asked to pursue that option. Figure 24.3a, b shows the finger deformity at presentation, and Fig. 24.3c 1 year after manipulation.

I have seen him most recently, almost 36 months after treatment, and found definite recurrence in the little finger proximal phalanx and some progression in the third and fourth ray midpalmar cords, but he has yet no significantly dysfunctional problems although he will continue to be followed.

Patient #4 represents a man in his seventh decade with a significant left little finger PIP joint contracture (Fig. 24.4). Figure 24.4a, b shows his deformity prior to treatment. Figure 24.4c depicts the hand 13 months after enzymatic fasciotomy and manipulation with near complete extension of the PIP joint and full flexion in all fingers. Figure 24.4d shows the hand at 18 months FU.

When he was next seen nearly 3 years (32 months) post injection, he demonstrated a contracture recurrence (Fig. 24.4d) but with a somewhat different cord, and most possibly, this could be considered "new disease" as well as a

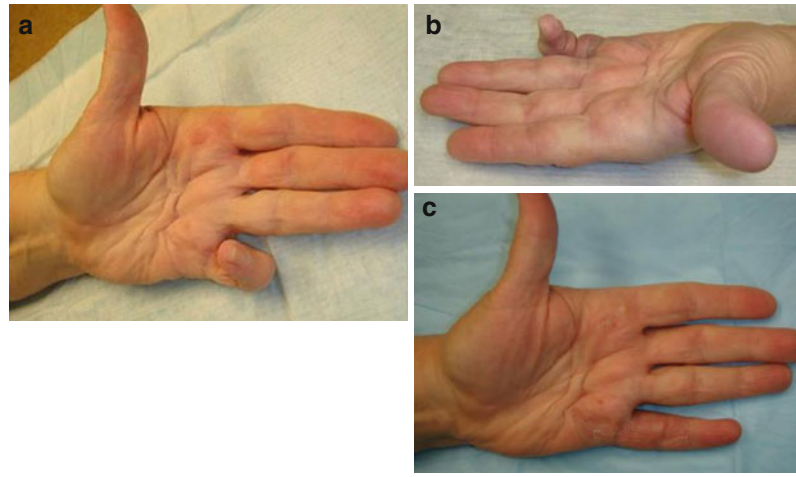

Fig. 24.3 Patient #3, treating recurrence after surgery. (**a**, **b**) Before injection. (**c**) 1 year after treatment

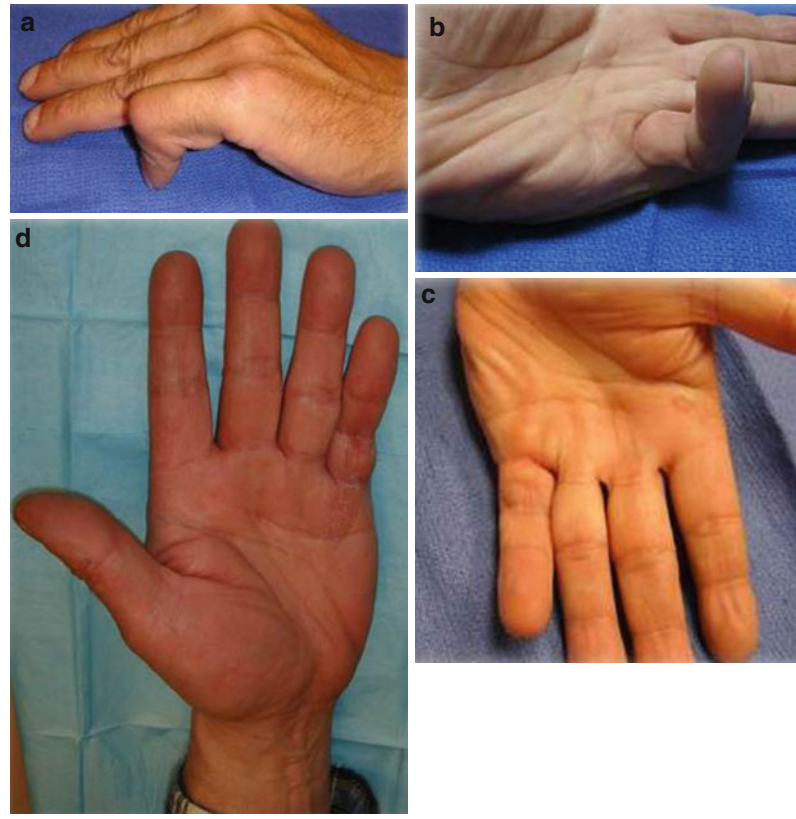

Fig. 24.4 Patient with recurrence. (**a**, **b**) Prior to CCH injection. (**c**) At 13 months F/U; (**d**) recurrence at 32 months F/U; (**e**) at 18 months F/U after the second injection cycle

"recurrent" (PIP joint) deformity. In any event, he was one of a series of patients who has been retreated with collagenase for recurrence after initial success. Figure 24.4e shows him at 18 months after the second collagenase intervention. He now has a residual PIP deformity of almost 20° but is very happy with his hand and retains full flexion. He told me he was fully prepared to have enzyme treatment again if it were warranted by new or recurrent deformity.

Conclusion

I have learned several things about treating Dupuytren Disease utilizing CCH but also having had decades of experience with surgery of variously aggressive and "minimally invasive" methods.

- *Local anesthesia is a critical component of office enzymatic fasciotomy.* Anesthetic can and should be administered before the enzyme, so the patient is not troubled by the endless needle pricks required in a single- or double-dose administration. Anesthesia is also essential at the manipulation visit before the manipulation. I routinely prefer its administration via palmar, flexor sheath, and intermetacarpal approaches. Local anesthetic in the injection field does not, in my experience, "dilute" or diminish the collagenase effects. I typically use an anesthetic containing 1:100,000 epinephrine except in patients with hypersensitivity or a cardiac history. I find that individuals of the age of the Dupuytren population already know when queried whether they are "sensitive or reactive to dental anesthetics" of the same type.
- Patience is necessary in effecting maximal correction. Flexing the MP joint to get PIP correction can be very helpful, especially with long-standing contractures and secondarily tight flexors. The lessons learned in surgery can be usefully applied to this nonsurgical method. Correction is a process.
- *Persistence of care and follow-up is necessary.* In my own experience, post collagenase splinting nightly for 3 months is the rule, not the exception. I can share, anecdotally but with complete assurance, that all the patients who have admitted to me that they "forgot" or "could not" use their night splints regularly had far less satisfying maintenance of improvement. Patients also need to understand that corrections deteriorate over time but, as an interested physician, I will also be there for them in the future.
- *Interphalangeal joint correction is reasonable, possible, and achievable with collagenase.* The fact that phalangeal anatomy has the flexors much closer to the cord has to be respected at enzyme instillation in order to minimize the risk of inadvertent sheath injection and tendon rupture. Injections must always be aimed "away from" the flexors and perpendicular to the cord.

Conflict of Interest Statement The author previously received research support from and served as a consultant to Auxilium Pharmaceuticals, Inc. However, the cases and opinions do not necessarily reflect the opinions, methods, or views of Auxilium, Endo, or Sobi. No funds or supports were received in conjunction with writing and preparation of this work; all illustrative cases are patients that the author has personally treated.

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Controversy: How to Treat Severe PIP Contractures? - Surgical Correction

25

Caroline Leclercq

Contents

25.1 Introduction

Contracture of the proximal interphalangeal joint (PIPj) is one of the most challenging problems in the treatment of Dupuytren Disease, especially when the flexion contracture is severe. A number of techniques, including needle fasciotomy, collagenase (CCH), fasciectomy, and dermo-fasciectomy, are currently advocated for the treatment of Dupuytren Disease. Our goal in the present controversy is to explain why the surgical treatment performs better than all other techniques.

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25.2 Definition

There is not an established definition of "severe" PIPj contracture, but one may agree that a flexion contracture of the PIP joint greater than 90° can be regarded as severe, and we have adopted his definition for this presentation (Fig. 25.1).

25.3 Treating a Severe PIP Contracture

Several problems need to be addressed when treating a severe PIPj contracture.

25.3.1 Skin

After release of the contracture, one will be frequently faced with a shortage of volar skin, especially if the skin was adherent to the nodules and cords.

Forceful correction after either needle or collagenase (CCH) treatment in severe contractures often creates a skin tear, which requires several

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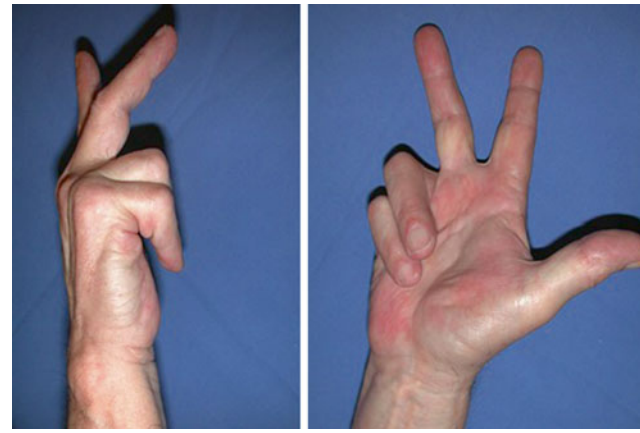

Fig. 25.1 Severe contracture of the two ulnar rays

weeks of dressing, thus losing part of the benefit of these nonsurgical treatments.

Surgery allows compensating for the skin shortage either with local skin flaps in 90° contracture with supple skin or with skin grafts when the contracture is greater, and/or the volar skin is scarred. Skin grafting in this case has a double objective: replace the missing skin and protect the area against recurrence.

In extremely severe cases, two-step procedures carry the advantages of softening and enlarging the skin before fasciectomy. Primary needle fasciotomy can be helpful in extending the MP joint in combined MP and PIPj contractures. In even more complex cases, preliminary distraction with an external fixator (TEC, S Quattro, Digit Widget, etc.) and then followed by fasciectomy may lead to satisfactory correction without skin problems (Rajesh et al. 2000).

25.3.2 The Patho-Anatomy of Dupuytren Fascia in the Finger

Whereas the nodules and cords in the palm are always superficially located, i.e., above the neurovascular pedicles and tendons, their patho-anatomy is complex at the digital level, with nodules and cords in different planes, including retrovascular and spiraling around the neurovascular pedicles. In the finger they are therefore much more difficult to reach with a percutaneous needle, and consequently neither needle fasciotomy nor CCH are likely to be fully effective. This is easily demonstrated in the literature: correction of the contracture is better with surgery than with the other two techniques (van Rijssen et al. 2006; Misra et al. 2007; Foucher et al. 2001). Nevertheless needle fasciotomy might be used to prepare severe cases for subsequent fasciectomy (Fig. 25.2).

Variable distribution of cords also puts the neurovascular bundle and even the tendons at risk with percutaneous techniques. Ultrasound has not proven very helpful, even with mini-probes, because of the flexed position of the joint and the possibility of isoechoic cords (Leclère et al. 2014; Uehara et al. 2013).

25.3.3 Joint Contracture

In severe long-standing Dupuytren contracture, the periarticular joint structures become involved in the contracting process, and the only way to release them is through surgery. Incision of the flexor sheath and of the check reins improves PIP extension in these cases. However one should not try to obtain full PIPj extension at all costs, and forceful maneuvers may be counterproductive, especially in arthritic joints, leading to a decrease of the ROM in flexion, far more impairing functionally than the lack of extension.

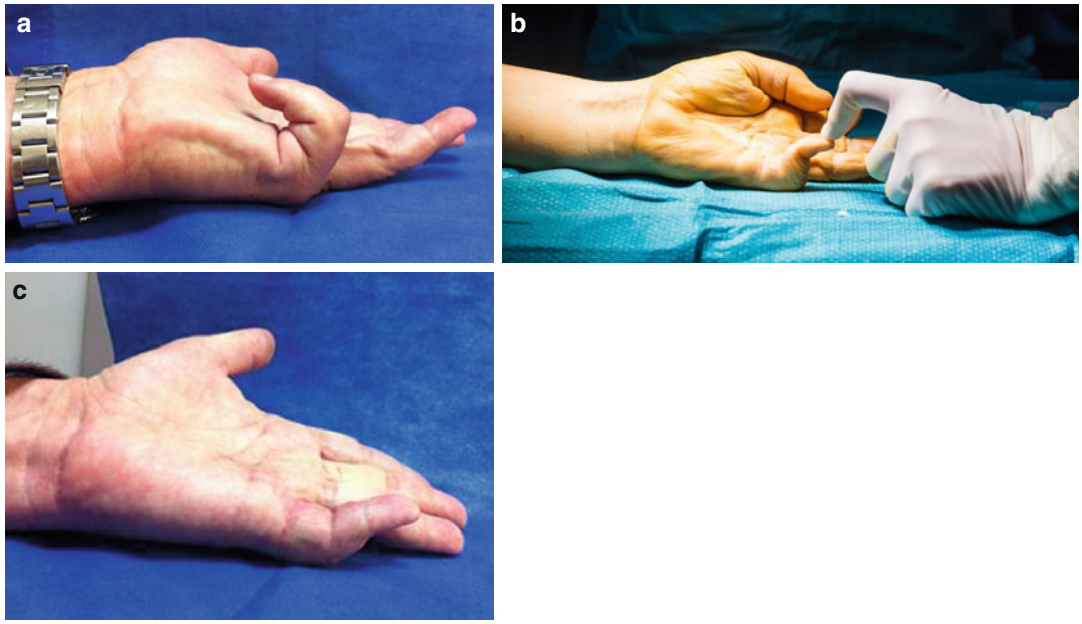

Fig. 25.2 Two-stage correction of severe PIPj contracture. (**a**) Preoperative view of severe isolated contracture of the 5th finger. (**b**) Primary needle fasciotomy of the MP joint: postoperative view. (**c**) Secondary fasciectomy: result at 4 months

25.3.4 Extensor Apparatus

In long-standing flexion contracture, the central band of the extensor apparatus may attenuate. This is obviated by the tenodesis test performed at the end of the procedure: full passive flexion of the wrist fails to provide PIP joint extension (Smith and Breed 1994; Smith and Ross 1994). This needs to be addressed by central band shortening and repair (if needed) or temporary K-wire immobilization in extension, the latter being our preferred way of treatment.

25.3.5 DIP Joint Hyperextension

Flexion contracture of the PIPj may lead to a reverse contracture of the distal interphalangeal joint (DIPj) in hyperextension. Sometimes this deformity can be treated by gentle manipulation after PIPj release, but in some cases, it requires surgical correction: release of the oblique retinacular ligament and/or distal tenotomy of the extensor apparatus (Tubiana 2000). Arthrolysis of the DIPj is rarely necessary.

25.4 Surgical Treatment

25.4.1 Surgical Details

Surgery of a severe contracted PIPj is not easy and requires attention to a number of details.

The skin flaps must be carefully planned to avoid skin necrosis, including wide angles, proximally based flaps, avoidance of undermining, and preventive skin grafting, when the cutaneous blood supply is too scarce. If the skin shortage is important, it is wiser to plan for skin replacement by a full thickness graft. Graft take is better over a bloodless field and a vascularized bed, therefore requiring tourniquet release and hemostasis and conservation of the flexor tendon sheath underneath the graft.

The neurovascular pedicles are particularly at risk, and the patient must be warned about the

Table 25.1 Complications after fasciectomy

Complications		Leclercq 2003	Bulstrode 2005	Denkler 2010	Becker 2010
No. of patients		155	253	41 articles (1988–2008)	43 articles (1950–2009)
Nerve injury	%	2	2	3.4	27
Arterial injury	%	3.3	0.8	2	?
Hematoma	%	0.4	2	2.1	35
Skin necrosis	%	2	(–)	22.9	?
Delayed healing	%	3.2	(–)		?
Infection	%	0	9.6	2.4	17
Lack of flexion	%	6.5	?	Stiffness 15.4	?
CRPS	%	0	2.4	5.5	32
Total	**%**	**14**	**18**	**3–39**	?

Complications are retrieved from two personal series (Leclercq 2003; Bulstrode et al. 2005) and from two literature reviews (Denkler 2010; Becker and Davis 2010)

risk of finger necrosis, especially in the index and 5th finger, where one of the two collateral arteries may be extremely thin.

The postoperative regimen includes physiotherapy and splinting in all cases of severe contracture. When a skin graft has been used, this is started after graft take is ascertained. Special attention is focused on recovering early PIPj flexion.

25.4.2 Complications

Complications of surgery of the severely contracted PIPj include skin slough, skin necrosis, laceration of nerves and arteries, stiffness, complex regional pain syndrome, and the dreaded finger necrosis. The rate of complications after fasciectomy varies greatly in the literature, from 3.6 to 39 % (Denkler 2010). Our own series involving 155 patients lead to 14 % complications. Literature reviews seems to indicate a trend toward a reduction in the reported percentage of complications in more recent years (Table 25.1) (Denkler 2010; Becker and Davis 2010).

Comparison with other techniques is very difficult because of the wide disparity in the recording of complications. In a randomized trial between needle aponeurotomy (NA) and surgical fasciectomy (SF) van Rijssen et al. (2006), report on 125 hands reports 55 % complications with NA, none of which were considered major, whereas there were only 30 % complications with SF, but 5 % were major.

A recent comparison of complications of CCH compared to the literature (Peimer et al. 2015) showed that the incidence of adverse events was numerically lower with CCH for some complications, but higher for others, and associated with transient complications specific of CCH.

25.5 Outcomes

The rate of recurrence varies greatly in the literature for three reasons: the lack of a common definition, the difference in scoring systems, and the lack of reference to the time factor. Recurrence specifically related to severe PIPj contracture has not been studied. However there is a consensus that the more severe the initial PIPj contracture, the most likely there is to be a recurrence (Misra et al. 2007).

A meta-analysis by Crean et al. (2011) indicates a higher rate of recurrence after needle aponeurotomy than after fasciectomy. When comparing recurrence rates available at 5 years in the literature (Foucher et al. 2001; Badois et al. 1993; van Rijssen et al. 2012; Tubiana and Leclercq 1986; Peimer et al. 2015), the figures seem to indicate a lesser rate of recurrence with fasciectomy, greater with CCH, and greatest with needle aponeurotomy.

The technique giving the least recurrence is dermo-fasciectomy. Not only recurrence is extremely rare under a skin graft (Tubiana and Leclercq 1986; Kelly and Varian 1992; Searle

and Logan 1992), but it seems to have a protective effect on the adjacent tissues on the same ray. From our series of 66 dermo-fasciectomies in severe cases, 23 were reviewed at an average of 5.6 years, with a recurrence rate of 21 %, never located under the skin graft.

Bullet Points

- Treatment of severe PIPj contracture is difficult.
- Fasciectomy is associated with better correction of the flexion deformity.
- Dermo-fasciectomy is associated with the least recurrence.
- Each technique is associated with potential complications, including finger necrosis, when trying to correct a severely contracted finger.

Conflict of Interest Declaration The author has no conflict of interest to declare.

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Part VI

Assessment

Tim Davis and Bert Reichert

26 Correlation of Function with Deformity in Dupuytren Disease: The Condition-Specific Southampton Scoring Scheme Outperforms the Generic QuickDASH

David Warwick

Contents

26.1 Background

Range of movement, which might have the advantage of objectivity and reproducibility, does not correlate well with function in Dupuytren disease (DD) (Degreef et al. 2009; Engstrand et al. 2009; Zyluk and Jagielski 2007). Therefore in Dupuytren research, angular deformity has only limited value as an outcome.

Thus, patient-related outcome measures (PROMs) should now be an integral part of research and hand surgery practice, but they must accurately reflect the underlying condition. The *QuickDASH* (QD) score (Beaton et al. 2005, Fig. 26.1) is widely used in hand surgery, but it is a generic score to cover all upper limb problems and so many of the domains (e.g. tingling, pain, sleep) are not affected in DD which will dilute its validity (Budd et al. 2011). Other schemes are more specific to DD such as the *Unité Rhumatologique des Affections de la Main scale* (URAMS) (Beaudreuil et al. 2011) but whether this captures all the relevant aspects of Dupuytren disease has been challenged (Rodriguez et al. 2015).

In an effort to find a scale which is more valid in DD, we developed the Southampton Dupuytren's Scoring Scheme (SDSS). This was derived by reducing many functional problems associated with DD into just five domains (Fig. 26.2), each relevant to DD (Mohan et al. 2014). In this study, we found that the SDSS had good internal consistency (Cronbach's alpha 0.87) and high test-retest reliability ($r=0.79$). In comparison with QD, it had favourable field characteristics and greater sensitivity to change (Standardised Response Mean SDSS −1.8; QD −1.2). Neither correlated well with goniometric deformity.

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*Quick*DASH

Please rate your ability to do the following activities in the last week by circling the number below the appropriate response.

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	UNABLE
1. Open a tight or new jar.	1	2	3	4	5
2. Do heavy household chores (e.g., wash walls, floors).	1	2	3	4	5
3. Carry a shopping bag or briefcase.	1	2	3	4	5
4. Wash your back.	1	2	3	4	5
5. Use a knife to cut food.	1	2	3	4	5
6. Recreational activities in which you take some force or impact through your arm, shoulder or hand (e.g., golf, hammering, tennis, etc.).	1	2	3	4	5

	NOT AT ALL	SLIGHTLY	MODERATELY	QUITE A BIT	EXTREMELY
7. During the past week, *to what extent* has your arm, shoulder or hand problem interfered with your normal social activities with family, friends, neighbours or groups?	1	2	3	4	5

	NOT LIMITED AT ALL	SLIGHTLY LIMITED	MODERATELY LIMITED	VERY LIMITED	UNABLE
8. During the past week, were you limited in your work or other regular daily activities as a result of your arm, shoulder or hand problem?	1	2	3	4	5

Please rate the severity of the following symptoms in the last week. *(circle number)*	NONE	MILD	MODERATE	SEVERE	EXTREME
9. Arm, shoulder or hand pain.	1	2	3	4	5
10. Tingling (pins and needles) in your arm, shoulder or hand.	1	2	3	4	5

	NO DIFFICULTY	MILD DIFFICULTY	MODERATE DIFFICULTY	SEVERE DIFFICULTY	SO MUCH DIFFICULTY THAT I CAN'T SLEEP
11. During the past week, how much difficulty have you had sleeping because of the pain in your arm, shoulder or hand? *(circle number)*	1	2	3	4	5

*Quick*DASH DISABILITY/SYMPTOM SCORE = $\left(\frac{\text{(sum of n responses)}}{n} - 1\right) \times 25$, where n is equal to the number of completed responses.

A *Quick*DASH score may not be calculated if there is greater than 1 missing item.

Fig. 26.1 QuickDASH

How much trouble do you have with:	No problem	Minor inconvenience	Modest inconvenience	Definitely troublesome	Servere problem
Discomfort					
Personal activities, *eg: washing face, dressing, washing hands, washing hair, putting on gloves.*					
Domestic activities, eg: *holding a glass/cup, opening jars, eating, cooking.*					
Work/Social interaction, *eg: using the computer, writing, shaking hands, cosmetic appearance.*					
Hobbies, *eg. driving/cycling, racket sports, DIY, playing musical instruments, gardening.*					
SCORE (Staff to complete)					

Fig. 26.2 Southampton Dupuytren's Scoring Scheme

26.2 Aim

The aim of this study is to correlate function with deformity in a different and larger cohort of patients with DD and in particular to determine which of the SDSS and QD fare better.

26.3 Materials and Methods

We studied the functional problems associated with 298 cords in 237 patients with Dupuytren contracture who had chosen, following a full explanation of the choices, collagenase *Clostridium histolyticum* (Warwick et al. 2015).

We measured the angle of deformity (i.e. extension loss) with a standard goniometer just prior to injection. 99 patients had an MCP contracture, 56 a PIP contracture, 47 a natatory cord (i.e. one palmar cord contracting two digits) and 96 cords with combined MCP and PIP contracture. In those with natatory and combined contractures, we summated the extension loss in each cord. Immediately prior we also asked the patient to complete the SDSS and the QuickDASH.

26.4 Results

We found that whereas there was no correlation between the QuickDASH and angular deformity (Fig. 26.3, $r=0.01$; $p=0.86$), there was a modest correlation between SDSS and angular deformity (Fig. 26.4, $r=0.2$; $p=0.002$).

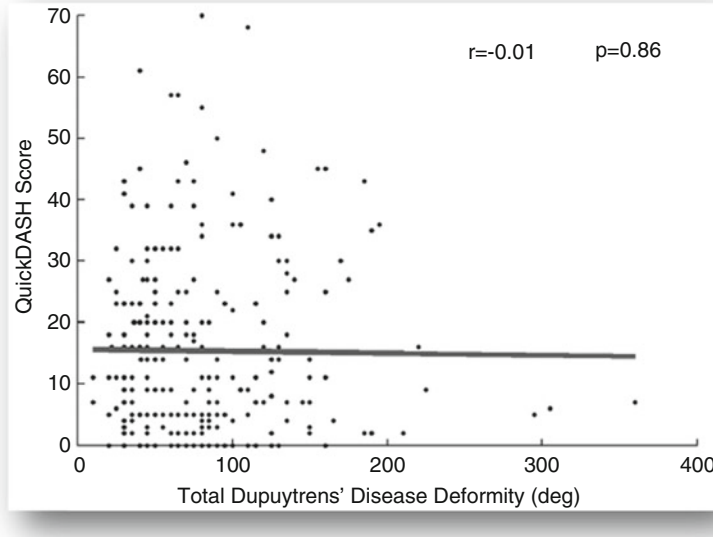

Fig. 26.3 Correlation between deformity and QuickDASH

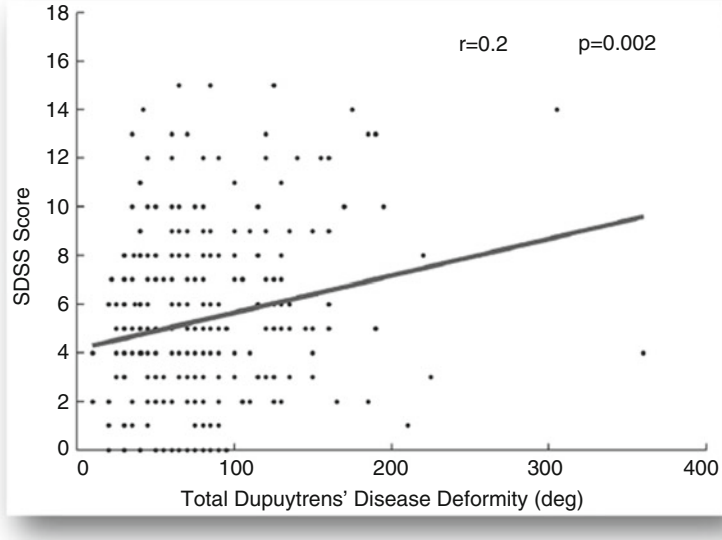

Fig. 26.4 Correlation between SDSS and deformity

26.5 Discussion

We have confirmed our previous observation in the development phase, with a new and larger set of patients that the Southampton Dupuytren's Scoring Scheme correlated better with deformity than the generic QuickDASH score. Nevertheless we are concerned that the score does not correlate very well with angular deformity. There are various reasons for this:

- Disability is multifactorial and so the angular deformity alone is probably not sufficiently sensitive.
- Patients may have several affected digits or other hand problems.
- Loss of flexion can be more of a problem than loss of extension in DD, particularly after surgery.
- Surgical complications can adversely affect a PROM even if the extension is corrected.
- Different digits have different effect on function – a flexion deformity of the little and ring fingers may have little effect on grip.

We would welcome independent validation of the SDSS which we believe may have a useful role in assessing the functional problems associated with DD. We would also encourage comparison with other condition-specific scores such as the URAM. We do not know the clinically important difference. And this demands further study before the real utility of a scheme such as SDSS is understood. Given the difficulties with generic scoring schemes in DD or specific DD scores, an alternative outcome measure in DD may be development of a patient-generated instrument in which the patient selects tasks with which they have difficulties due to DD and then rescores these after treatment.

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Figures 26.3 and 26.4 are reproduced with permission from the Journal of Hand Surgery European, in which they were published in a letter to the editor (*J Hand Surg Eur* 2015:40:544).

The author has no conflicts of interest to declare.

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Tonometry as an Outcome Measure for the Treatment of Early Dupuytren Disease

27

Catherine Ball, David Izadi, and Jagdeep Nanchahal

Contents

27.1 Introduction

Dupuytren Disease (DD) is a common fibroproliferative disorder of the hand affecting 4 % of the general UK and US populations (Hindocha et al. 2009). The classic description of disease progression is the initial appearance of pitting of the palmar skin and nodules characterised by high cellularity and cell proliferation with subsequent matrix deposition to form cords. This is followed by a final fibrotic stage that is associated with maturation of the cords and digital contractures affecting one of more digits resulting in significant impairment of hand function (Rombouts et al. 1989). Early DD is generally described by the presence of palmar nodules with limited or no contracture of the digits although there is currently no uniformly accepted clinical definition of early disease (Nanchahal and Izadi 2016). Surgery is usually considered when a digit is flexed to 30° or more at the metacarpophalangeal joint or any degree of flexion of the proximal interphalangeal joint.

27.1.1 Clinical Measurement of Early Disease

Early DD is generally described by the presence of palmar nodules with limited or no contracture of the digits. The ideal treatment for this disorder would address this early stage and prevent progression to digital flexion contractures. Various

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treatments have been proposed including intralesional steroid injections, physical therapy and radiotherapy. However, there is no accepted measure to assess their efficacy. Objective measurements of joint angles can only be used to assess progression of deformity but do not register regression or disease progression, recurrence or progression before the development of deformities. Many studies describing the treatment of patients with early disease have used clinical descriptors for nodule hardness. Examples include:

- Fibrosis softer or diminished (Zachariae and Zachariae 1955)
- Softening of nodules (Finney 1953, 1955; Lukacs et al. 1978)
- Tissue softer (Markham and Wood 1980)
- Consistency of palpable nodules (Keilholz et al. 1996)
- Nodule easier to inject (Ketchum and Donahue 2000)
- Less hard (Grenfell and Borg 2014)

27.1.2 Objective Measurement of Skin Involvement

Objective measurement of tissue hardness in DD has been advocated, and it was proposed that efficacy of treatment might be assessed by tonometry (Eaton 2012). Tonometry measures the resistance of tissue to compression using a handheld mechanical gauge which is placed on the patient's skin and has been used clinically to evaluate tissue hardness (firmness) of cutaneous scars (Magliaro and Romanelli 2003), scleroderma (Merkel et al. 2008) and lymphoedema (Chen et al. 1988). An ophthalmic tonometer was used to evaluate skin compliance before and 2 years after Z-plasty without fasciectomy in 16 patients with Dupuytren Disease (Thurston 1987). The data indicated that the compliance of the skin overlying the Dupuytren tissue was 'softer' after Z-plasty and similar to that of normal skin.

27.2 Material and Methods

We performed a prospective study to determine whether tonometry can be used to assess the hardness of the nodules in patients with early Dupuytren Disease compared to the equivalent anatomical sites in healthy age and sex-matched volunteers. Ethical approval was attained and all participants gave informed written consent (REC reference: 11/SC/0447). Tissue hardness was measured using a RX-1600-OO type OO durometer and expressed in arbitrary units from 0 to 100, with 100 being the maximal hardness (Fig. 27.1). Prior to commencing the study, we

Fig. 27.1 Tonometry measurement (illustration of the tonometer in use)

developed a protocol for using the durometer in order to minimise intra- and inter-observer variability and trialled this in 3 individuals with early disease and two healthy volunteers. The participants' forearm and hand was supported on a high table enabling the observer to view the tonometer dial at eye level. The tonometer was held perpendicular to the skin using a 2 handed technique supporting above the midline of the dial to ensure that it was balanced on the skin without application of external pressure by the observer. Each reading was recorded as soon as the needle on the dial became steady.

For the study we defined early disease as flexion deformities of ≤30° at the metacarpophalangeal or at the proximal interphalangeal, with a maximum total flexion deformity of 45° equivalent to Tubiana stage 1.

Two independent assessors measured all patients using the agreed standardised protocol. Nodules to be assessed were identified and agreed by both assessors for each DD patient, marked on the hand and recorded on a diagram on the reporting sheet. Measurements for all healthy volunteers were taken at 3 predefined and marked palmar and digital locations according to the protocol. Each assessor was blinded to the score recorded by the other. Measurements were taken during the same session by each assessor in turn for all participants. Three measurements were recorded for each participant at the selected site on the palm or digit. Statistical analysis was performed using the PRISM statistical software programme. Inter-observer was calculated using Pearson's correlation coefficient (95 % CI). Normal distributions of data were confirmed using the D'Agostino and Pearson omnibus normality test. Data for patients with DD and healthy volunteers were compared using an unpaired *t*-test.

27.3 Results

Thirty-seven participants were recruited to the study: 25 patients with Dupuytren Disease and 12 healthy volunteers. The ages of the healthy volunteer (mean ± SEM, 61.4 ± 3.1 years) and the patients with Dupuytren Disease (64.5 ± 2.1) were similar, as was the ratio of male to female patients in both groups (3:1). The demographics are summarised in Table 27.1.

We found that the tonometer readings for the Dupuytren patients were higher compared to the matched healthy volunteers (Table 27.2).

Inter-observer reliability was high, with an intraclass correlation coefficient of 0.96 (95 % confidence intervals 0.942–0.967) $p<0.0001$ (Fig. 27.2).

27.4 Discussion

Our data show that tonometry can be used to objectively evaluate the hardness of palmar tissues. Tissues in patients with early Dupuytren Disease were significantly harder than corresponding sites in sex- and age-matched healthy controls. The protocol we used for measurement showed high intra- and inter-observer reliability in individuals with early Dupuytren Disease. This is consistent with previous reports in patients with localised sclerosis (Seyger et al. 1997) and hypertrophic scarring (Magliaro and Romanelli 2003) and when tonometry was used as an outcome measure in a multicentre randomised clinical trial of treatment of early systemic sclerosis (Merkel et al. 2008). We propose that tonometry

Table 27.1 Table showing numbers of study patients and healthy volunteers with age ranges

Participants	Patients	Patients mean age (range)	Healthy volunteers	Healthy volunteers mean age (range)
Male	19	64.9 (43–82)	9	60.2 (49–79)
Female	6	63.2 (54–70)	3	65 (51–72)
Total	25	64.5 (43–82)	12	61.4 (49–79)

Table 27.2 Table showing results of tonometry readings and extension deficit for patients and healthy volunteers

	Dupuytren Disease, affected hands only (mean ± SEM) $n = 25$	Healthy volunteers, both hands (mean ± SEM) $n = 12$	p value
Tonometry	Mean 53 ± 8	Mean 32 ± 3	<0.0001
Extension deficit (MCPJ + PIPJ)	11° ± 20°	1° ± 2°	0.0018

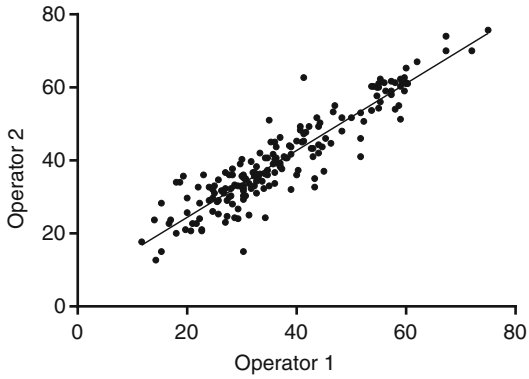

Fig. 27.2 Correlation of tonometry in Dupuytren Disease and controls performed by 2 independent observers (each point represents the mean of 3 readings taken at the same site by 2 independent assessors. Pearson $r = 0.9240$. $p < 0.0001$)

should be used for assessing nodule hardness when evaluating treatments for early DD rather than relying on subjective clinical assessment alone. However, further studies are required to evaluate whether the technique is sufficiently sensitive to detect change in nodule hardness following treatment.

27.5 Conclusions or Bullet Points

- Tonometry can be used to objectively evaluate nodule hardness in patients with early DD.
- We have described a protocol for measurement that shows high intra- and inter-observer reliability.
- Further studies are necessary to assess sensitivity to change following treatment of DD nodules.

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28 The Intra- and Interobserver Agreement on Diagnosis of Dupuytren Disease, Measurements of Severity of Contracture, and Disease Extent

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28.1 Introduction

Treatment of Dupuytren Disease is primarily aimed at decreasing the flexion deformities of the fingers. Although there are various treatment options (van Rijssen and Werker 2009), the majority of the patients are treated using partial fasciectomy (Au-Yong et al. 2005). The recurrence rates of Dupuytren Disease are high, ranging from 21 to 85 %, depending on the type of treatment (van Rijssen et al. 2012; Peimer et al. 2013).

Clinicians often decide to treat a patient based on the amount of extension deficit of the fingers (Au-Yong et al. 2005). However, the reliability of these goniometry measurements is unclear. Only one paper reported the reliability of goniometry of the fingers of Dupuytren patients (Engstrand et al. 2012). Unfortunately, this was only reported for active extension deficit, while the passive extension deficit is often a decisive factor in the choice of treatment (Hurst 2011).

The passive extension deficit is often classified using the Tubiana classification (Tubiana 1986). However, in the general population, the majority of the patients have only mild disease (stage N) without flexion deformities (Gudmundsson et al. 2000; Degreef and De Smet 2010; Lanting et al. 2013). Disease progression cannot be measured using goniometry in this group. Two previous studies report an alternative

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measurement method, where the nodules and cords are encircled and registered using a photocopy of the hands (Herbst and Regler 1986; Seegenschmiedt et al. 2001). However, it is unclear how the disease extent was quantified in these studies. Therefore, we used a tumorimeter to determine the size of nodules and cords. If this new measurement is reliable, it can be used to determine progression of disease in cases without flexion deformities.

This study was aimed to determine the intra- and interobserver agreement of four different measurement variables for diagnosing DD, determining severity of flexion contracture and disease extent, namely, (1) the diagnosis itself, (2) Tubiana stage, (3) total passive extension deficit measured with a goniometer, and (4) the area of nodules and cords measured with a tumorimeter.

28.2 Methods and Materials

28.2.1 Participants

Seventy-seven adults with primary DD in at least one hand were asked for participation (Zou 2012). Those who were willing to participate gave written informed consent. Approval of the medical ethics committee of the University Medical Center Groningen was obtained before starting the study.

28.2.2 Outcome Measures and Instruments

Dupuytren Disease was diagnosed by physical examination of the hands. The diagnosis was recorded binary for each finger separately.

Total passive extension deficit (TPED) was measured in degrees using a Rolyan flexion-hyperextension finger goniometer (Smith & Nephew, Hull, UK). TPED was obtained by adding the passive extension deficits of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints together. Passive extension deficits were measured following the procedure described in Broekstra et al. (Broekstra et al. 2015).

TPED was transformed into a stage, using the classification system of Tubiana (Tubiana 1986).

A tumorimeter (Pfizer Oncology, Pharma-Design Inc., China, Fig. 28.1) was used to determine the surface area of round-shaped nodules in square centimeters. To determine the area of other shaped nodules or cords, the length and width were measured using the caliper on the tumorimeter.

28.2.3 Procedure

All measurements were done by two observers. One of the observers was a medical doctor with extensive experience in diagnosing Dupuytren Disease. The other was a human movement scientist, who was trained to recognize Dupuytren Disease (Broekstra et al. 2015).

First, measurements were taken only by the first observer. To determine the intra-observer agreement, the participants returned 2–4 weeks later for the second measurement by the first observer. To determine the interobserver agreement, the participants were measured by the second observer immediately after the measurements of the first observer. The same procedure and measurement instrument were used in all measurements.

28.2.4 Statistical Analyses

To determine the agreement on the continuous variables (TPED, area of nodules and cords), using a one-way random effect model was used, whereafter the ICC was calculated. Only fingers with agreed positive diagnosis were used in these analyses.

The agreement on diagnosis and Tubiana stage was determined by calculating the ICC,

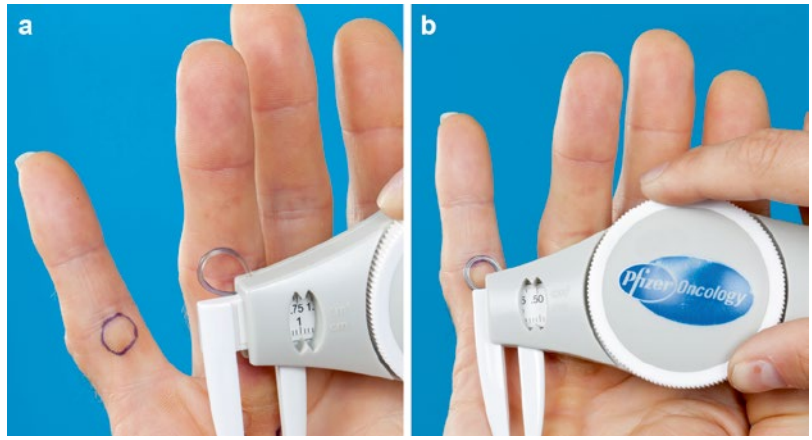

Fig. 28.1 Use of the tumorimeter. (**a**) The nodule is encircled, (**b**) the loop is placed over the nodule, whereafter the surface area can be read off

using a latent variable underneath the binary or ordinal outcome. Detailed information on the statistical analyses is found in Broekstra et al. (Broekstra et al. 2015)

28.3 Results

A number of 54 patients (33 men and 21 women) agreed to participate, having 78 primary affected hands. Their mean age was 65.8 ± 9.2 years. Agreed positive diagnosis of Dupuytren Disease was found in 194 fingers, while in 8 fingers there was no consensus between the observers about the presence of Dupuytren Disease.

The agreement for diagnosis was very good (Altman 1991), ranging from 95.5 to 99.9 % for the intra- and interobserver agreement.

The agreement on Tubiana stage ranged from 73.5 to 98.9 %. Specified results are reported elsewhere (Broekstra et al. 2015).

For the other outcome measures, the agreements were good overall (Table 28.1). Measurements of TPED in the left middle fingers were lower than average. This was also the case for measurements of area of nodules and cords in the left middle finger. The intra-observer agreement was higher on average than the interobserver agreement.

28.4 Discussion

The results of this study show that overall, diagnosing Dupuytren Disease, measuring the severity of contracture (TPED and Tubiana), and disease extent (area of nodules and cords) have a high intra- and interobserver agreement.

The agreement in diagnosis was not 100 %. This indicates that there are always cases in which there is uncertainty about the presence of Dupuytren Disease, despite experience of the observer.

With respect to TPED, the intra- and interobserver agreement was very good (Altman 1991), indicating that reliable values can be obtained when consecutive measurements are taken by the same or another physician in clinical practice. Although both agreements of TPED were good overall, the agreements in the left middle fingers were lower than in the other fingers. Right-handedness of the observers or dynamism (Rodrigues et al. 2015) might form an explanation for this finding.

Intra- and interobserver agreement for the measurements of area of nodules and cords were good to very good in all fingers, except for the left middle finger and right thumb. The lower agreement in the thumb might be explained by the anatomy of the thumb and first web space: the distal and proximal transversal commissural

Table 28.1 Intraclass correlations and 95 % CI for each outcome variable, presented for each hand and finger separately

	Intra-observer agreement		Interobserver agreement	
	Left	Right	Left	Right
TPED				
Thumb	NA[a]	NA[a]	NA[a]	NA[a]
Index finger	96.0 [84.6; 99.9]	99.5 [98.4; 100.0]	92.3 [71.1; 99.9]	92.3 [74.3; 99.7]
Middle finger	47.9 [15.8; 81.1]	92.2 [84.9; 97.2]	45.0 [12.9; 79.9]	85.2 [72.5; 94.5]
Ring finger	99.8 [99.6; 99.9]	91.0 [84.6; 95.8]	96.1 [92.9; 98.3]	92.8 [87.7; 96.6]
Little finger	97.4 [94.6; 99.2]	94.8 [90.2; 98.0]	98.5 [96.8; 99.5]	96.8 [93.7; 98.9]
Area of nodules and cords				
Thumb	82.2 [65.0; 94.4]	50.8 [17.4; 83.8]	72.9 [49.4; 90.9]	63.3 [32.4; 89.0]
Index finger	98.6 [94.5; 100.0]	95.2 [83.8; 99.8]	96.7 [87.0; 100.0]	95.9 [85.8; 99.9]
Middle finger	82.9 [65.6; 94.9]	88.0 [77.1; 95.6]	48.4 [16.3; 81.3]	69.3 [47.1; 87.5]
Ring finger	97.1 [94.8; 98.8]	95.8 [92.7; 98.1]	90.6 [83.4; 95.9]	93.0 [88.0; 96.7]
Little finger	93.8 [87.3; 98.0]	91.9 [84.8; 96.8]	87.6 [75.7; 95.9]	93.6 [87.4; 97.8]

[a]Not applicable, since TPED was not measured in the thumb

ligaments can easily be mistaken for Dupuytren cords (Tubiana et al. 1982; Rayan 2003).

Conclusion

Diagnosing Dupuytren Disease and determining the disease extent and severity of flexion contracture using Tubiana classification, TPED, and the area of nodules and cords have a high intra- and interobserver agreement. This agreement is high in general, but measurements are more difficult for the thumb and middle finger. In addition, the newly introduced measurement of the surface area of nodules and cords has a high agreement and is suitable for studying disease extent in cases without flexion deformities.

Conflict of Interest Statement For this chapter the authors have no conflict of interest to declare.

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Variation in Range of Movement Reporting in Dupuytren Disease

29

Anna L. Pratt and Catherine Ball

Contents

The literature was systematically reviewed with the aim of establishing robust methodology for measuring and reporting range of movement in Dupuytren Disease. Following screening, 90 studies met the inclusion criteria. A total of 24 different descriptors were identified describing range of movement in the 90 studies and 16 stated the use of a range of movement protocol. Eight of the 24 categories were identified as possibly describing the same measure, 'lack of joint extension', and together accounted for the most frequently used.

Published studies lack clarity in reporting range of movement, preventing data comparison and meta-analysis. It is recommended that range of movement measuring and reporting for Dupuytren Disease requires transparent reporting using a stated published range of movement protocol.

29.1 Introduction

Hand function in Dupuytren Disease is usually assessed using a range of both physical measures and questionnaires. Range of movement (ROM) has already been reported as the most commonly used outcome measure within Dupuytren Disease literature (Ball et al. 2013). A goniometer is a quick, easy and portable tool to assess ROM and has been reported to be an objective and reliable measure (Adams et al. 1992). The challenge that arises from using such a universally recognised tool is the lack of agreed assessment methodology for Dupuytren Disease and reporting guidelines. This has resulted in a variation of methods being used to measure and report outcomes thus inhibiting comparative analysis.

The hand is a complex structure involving the orchestration of combined movements that

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enable it to have the capacity for strength, dexterity and expression. The complexity of the hand is in contrast to the simplicity of the planes of movement achieved by the digits. The three finger joints (MCP, PIP and DIP) all have the ability to flex and extend, and it is predominately this ability that is affected in Dupuytren Disease. Consequently it is these movements that should be measured and reported to identify change.

To date, the lack of consistency in Dupuytren Disease ROM measurements and variation in measures used has presented difficulties when comparing studies' findings. In order to identify the current variation in methodology used in Dupuytren Disease, the literature was systematically reviewed. The aim was to recommend robust methodology for use in future studies.

29.2 Material and Methods

A PICOS analysis is a method used to identify a clinical research question. This was carried out as illustrated in Table 29.1 for primary or recurrent Dupuytren Disease range of movement. A literature search was conducted using the predetermined search criteria of databases for the last 20 years (Ovid Medline, Ovid EMBASE, CINAHL, PubMed) and relevant studies were systematically reviewed.

Publications were suitable for inclusion if the participants had received a surgical treatment, percutaneous fasciotomy or collagenase injection for Dupuytren Disease, if the ROM data was able to be analysed and if articles were published in English within the last 20 years.

29.3 Results

A total of 638 publication titles were screened following removal of duplicates. Relevant abstracts were assessed using a screening tool resulting in 548 publications being excluded. Full text was obtained for the remaining 90 studies.

All 90 studies were reviewed and the method of ROM methodology was extracted and tabulated on a graph. A variation of 24 ROM descriptors was identified with percentage change being the most frequently used as illustrated in Fig. 29.1.

Table 29.1 PICOS analysis used to search the literature

PICOS analysis	Definition
Participants	Dupuytren Disease of the hand
Intervention	Surgical treatment/percutaneous fasciotomy/collagenase injection for DD
Comparisons	Not applicable (systematic review)
Outcomes	Reported range of movement
Study design	Included: RCTs, non-randomised CCTs and case series Excluded: case studies, reviews and conference papers

Further analysis revealed that 8 of these 24 ROM descriptors were potentially describing the same measure, extension deficit:

- Flexion contracture
- Joint contracture
- Joint extension deficit
- Extension deficit
- Extension contracture
- Flexion deformity
- Contracture
- Extension of a joint

This was confirmed when the 8 categories were scrutinised revealing that each measure was used only once in each publication.

Although the majority of studies reported ROM measurements in degrees, it was not always clear if a goniometer had been used to assess ROM objectively. Furthermore, there was ambiguity whether measurement had been taken actively or passively as both measures are relevant to Dupuytren Disease.

Goniometry was specified as being used in 43 of the 90 studies. On closer evaluation of these studies, only 16 (Anwar et al. 2007; Beyermann et al. 2004; Budd et al. 2011; Donaldson et al. 2010; Engstrand et al. 2009; Gilpin et al. 2010; Herweijer et al. 2007; Hurst et al. 2009; Jerosch-Herold et al. 2011; Johnston et al. 2008; Midgley 2010; Misra et al. 2007; Pess et al. 2012; Skirven et al. 2013; Witthaut et al. 2013; Zyluk

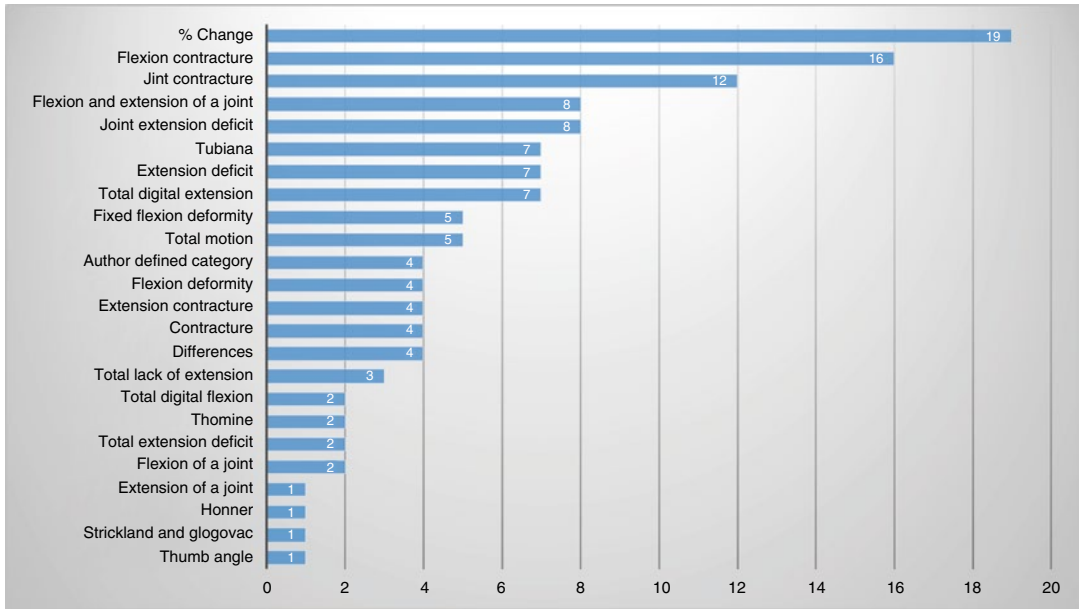

Fig. 29.1 Variation of measures used by description ($n = 24$)

and Jagielski 2007) described how measurement was assessed in a way that would permit replication for comparison purposes. This included one study that unusually defined a fully extended joint as 180° on the goniometer (Witthaut et al. 2013). However, as the method was fully described, comparison with other studies, using zero as full extension, was possible.

Only two studies (Donaldson et al. 2010; Skirven et al. 2013) reported testing for intrinsic tightness affecting the PIP joint. Assessing the extended PIP joint with MCP held in flexion enables a true representation of the PIP joint capability.

29.4 Discussion

One of the main areas of concern arising from the analysis was the omission of a measurement protocol in the majority of studies.

Hyperextension is of interest clinically but inclusion of hyperextension in ROM analysis may result in misleading data. This is particularly evident when used in a composite measure, such as total active motion (TAM). The difficulty arises when the negative hyperextension data can hide a deformity or skew analysis. In addition it does not identify where change specifically occurs. If desired TAM reporting could be used but full ROM data for each joint should always be reported and methods should clearly state whether negative hyperextension values are included in the calculation. Minimising bias in ROM is also a concern. This has been raised when considering dynamism (Rodrigues et al. 2015) as the position of the joints can affect the ROM.

Conclusions

These results highlight that ROM measuring and recording for Dupuytren Disease require standardisation to enable comparability of results in future practice.

To assist future practice, an agreed published ROM protocol using a goniometer should be used. This will also help to achieve a consensus on terminology to report the extension deficit at a joint. We recommend transparent reporting of active and passive digital flexion and extension of each joint, with the additional measure of active PIP extension with the MCP held in flexion (intrinsic tightness). This also has the added benefit of minimising the effect of dynamism as described by Rodrigues et al. (2015).

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30 Use of Digital Photography and Mobile Device Application to Assess Finger Deformity in Dupuytren Disease

Daniel Gheorghiu and Vijay Bhalaik

Contents

30.1 Use of Newer Goniometric Techniques

Georgeu et al. compared computer-aided goniometry with standard goniometry for finger joint angles already in 2002. They measured 109 finger joint angles at the extremes of flexion and extension and found a good correlation between the two methods, however, noted that computer goniometry averaged 1° more than the standard goniometry (Georgeu et al. 2002).

Hoffmann et al. (2007) measured upper limb range of motion with an Internet-based goniometer in people who have a stroke, and their results suggest that therapist can confidently use the Internet-based goniometer for remote upper limb range of movement measurements.

In 2010 Carey et al. examined the reliability, validity and clinical usability of a digital goniometer. In their research they involved 5 therapists who measured 5 joint motions in a total of 18 healthy subjects with a universal goniometer and a digital goniometer. They showed no statistically significant difference in intra- or inter-rater reliability between the devices.

Blonna et al. (2012) examined if digital photography-based goniometry is as accurate and reliable as clinical goniometry for measuring elbow range of motion and found this to be true. They concluded that their study validates an objective measure of patient outcome without requiring doctor-patient contact.

Crasto et al. (2015) analysed photograph-based clinical goniometry to visual estimation and manual goniometry in their comparative study involving 8 motions of the upper extremity in 69 patients. They conclude that their study supports photograph-based goniometry as the new standard goniometric technique which additionally allows better documentation of measurements and potential incorporation into medical records.

Krause et al. (2015) examined the reliability and accuracy of a goniometer mobile device application for video measurement of the functional screen deep squat test. Twenty-six healthy subjects

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performed three functional movement screen deep squats recorded simultaneously by both the app (on an iPad [Apple Inc]) and the 3D motion analysis system. The app video was analysed frame by frame to determine, and freeze on the screen, the deepest position of the squat. With a capacitive stylus, reference lines were then drawn on the iPad screen to determine joint angles. They concluded that the 2D app demonstrated excellent reliability and may be used as an alternative to a sophisticated 3D motion analysis system.

Another study from Otter et al. published in 2015 also looked at the reliability of a smartphone application to measure first metatarsophalangeal joint motion when compared to a universal goniometer. They too found a higher reliability of measurements when using the smartphone application but concluded that devices should not be used interchangeably as significant variations in measurement between devices may occur.

30.2 Assessment of Dupuytren Contracture

As shown previously many studies exist in the literature comparing the use of newer goniometric techniques to the more traditional manual or universal goniometric technique.

Only one study in 2009 examined the use of photography-based goniometric contracture measurements specifically in Dupuytren Disease. Smith et al. compared computer software-aided estimation of Dupuytren contracture to clinical goniometric measurements. Firstly the contractures were measured using a finger goniometer. Then, digital photographs of the contracted fingers were visually assessed and the degree of contractures estimated. Lastly, the degree of contractures was measured using a computer program. They found that the visual estimations correlate well with clinical goniometric measurements and improve further if measured with computer software (Smith et al. 2009).

Gheorghiu et al. used digital photography and a mobile device application compared to standard goniometry to assess finger deformity in Dupuytren Disease. They obtained photographs of the hand of 18 patients with Dupuytren contractures involving the metacarpal-phalangeal (MP) – and the proximal phalangeal (MP) joint of the little finger. The contractures were initially measured by a doctor and a physiotherapist using standard goniometry and reassessed using a mobile device application (Fig. 30.1). Exclusion criteria were deformities of any other finger (details will be published elsewhere). Although they found no statistical difference between the techniques, they too noted an overestimation of the deformity with the mobile device application (Gheorghiu et al. 2015).

30.3 Discussion

It is estimated that smartphone applications will enable the mobile Health (mHealth) industry to successfully reach out to 500 million of a total 1.4 billion smartphone users globally in 2015 (Jahns 2010).

Not only are consumers taking advantage of smartphones to manage and improve their own health, a significant number (43 %) of mHealth applications are primarily designed for healthcare professionals. These include CME (continued medical education), remote monitoring and healthcare management applications (Jahns 2010).

Kuegler et al. investigated applications using the goniometer function in smartphones, to analyse their availability, reliability and validity versus a universal manual medical-grade goniometer

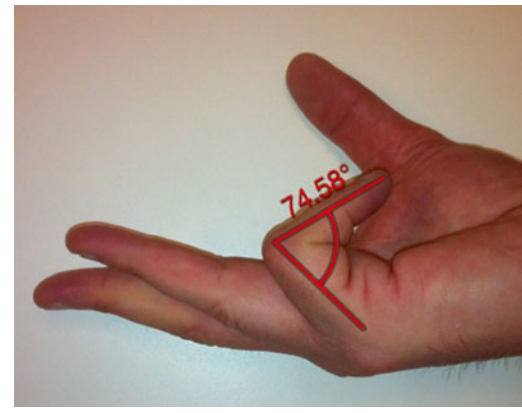

Fig. 30.1 Mobile device application measurements of Dupuytren contracture. With the aid of the mobile device application, lines are superimposed of the mid-axes of the affected fingers as judged by the assessor. The application then automatically calculates the angle between the lines

in hand surgery and their applicability in daily clinical practice. They found that 87.5 % (14 out of 16) of the tested applications were comparable to the mechanical goniometer and therefore reliable and valid for measuring angles. They furthermore report that, of the tested applications, no clinical studies related to hand surgery and that so far no Android application was evaluated in a clinical setting (Kuegler et al. 2015).

The available literature supports the use of photography-based and/or computer- and application-aided goniometry, and with today's technology-keen generation, it could be speculated that it would be easier to find an available smartphone than a standard goniometer in a clinical setting.

The benefit to use a photogoniometer application on a mobile device is the possibility for storing the picture for documentation in medical health records provided there is an institutional agreement on data protection.

It may even be possible that this technology could be used for remote monitoring of patients with Dupuytren Disease in the future.

However, some limitations of photogoniometric measurement should be considered.

Although the small finger is a typical site of the disease, others – mainly the ring finger – are also affected. These fingers are difficult to evaluate with the little finger always being in the way.

The orientation of the camera needs to be standardised: the optical axis of the lens has to be perpendicular to the plane of the moving finger, ideally being the rotation axis of the joint being examined. This might be difficult to achieve, especially when photogoniometric measurements are being performed remotely.

Conclusions

- Dupuytren contracture can reliably be measured with a photography-based and computer- or application-aided method.
- Digital measurement may overestimate the degree of contracture.
- Avoid variations of measurement by the consistent use of one application or software program.
- The orientation of the camera needs to be standardised.

Conflict of Interest Declaration The authors have no conflict of interest to declare.

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31 Application for Determining the Degree and Diagnose Code of Dupuytren Contracture by Digital Photography

Andrei Zhigalo, Anton Lesniakov, Hvan Innokentiy, Alexander Silaev, Victor Morozov, and Vitaliy Chernov

Contents

31.1 Introduction

Measuring extension deficits of Dupuytren contracture is a continuing challenge, specifically if it is done by patients without the support of a doctor. Photography can be used to develop standardized evaluation methods and recording. Recently, the use of computer-aided methods to measure angles has increasingly been researched and showed promising results (Blonna et al. 2012; Crast et al. 2015). The quickly growing availability of mobile devices makes those an excellent means for measuring the extension deficit in Dupuytren Disease, provided suitable and easy to use software is available (Kuegler et al. 2015). The application presented here has been designed for easy and reproducible measurement. The software is running on Windows and Apple OS, i.e., on PCs, tablets, or smartphones.

31.2 How the Application Looks Like (User Interface)

The user interface consists of two zones on the screen. The working zone is in the left part of the screen and is divided into an upper and a lower part by a horizontal line (Fig. 31.1). The upper part shows the loaded photo of the hand in lateral projection (Georgeu et al. 2002). The lower part shows a diagram with an example where to mark joints on the photo. These marks are required for

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joint positioning and contracture measurement. A healthy hand is being used as example because patients found that easier to understand.

The second zone (primary zone) is located in the right part of the screen. It contains buttons for loading ("Upload") and selecting previously loaded photos ("Choose"), a menu for choosing the finger ("Finger"), a window where measured extension deficits for MP, PIP, and DIP joints are listed ("Measurements"). The section "Total" shows the sum of the extension deficits over all joints (Total Passive Extension Deficit=TPED). Stage shows the calculated stage of contracture according to Tubiana's classification. Dx shows the coded summary for diagnosis. A view of the user interface is also available on http://dupuytren.medesse.com.

31.3 Using the Application

To start you need to take a picture of the patient's hand from the lower third of the forearm to the fingertips in strictly lateral projection from the little finger. The hand should be lying palm upward on the desk in the position of maximum extension of the fingers. For better picture quality, the hand and fingers should be well highlighted. After a good shot, the picture is uploaded by pressing the Upload button. Next on the picture, the joints are marked by properly positioned dots for evaluating the extension deficit. The dots can be selected by the cursor and moved to the correct position on the finger (see *5* in Fig. 31.1). The lower half of the working zone illustrates correct positions schematically. When the dot is placed in the correct position, it changes its color to green; if it is placed wrongly, it is red. When the marking is completed, i.e., all dots are green, the program automatically determines the disease stage and the extension deficits and encrypts the diagnosis for every code.

31.4 Verifying Measurement Results

In order to understand where the fingers are to be measured best and how reproducible and reliable the measurement results are, two test series were performed.

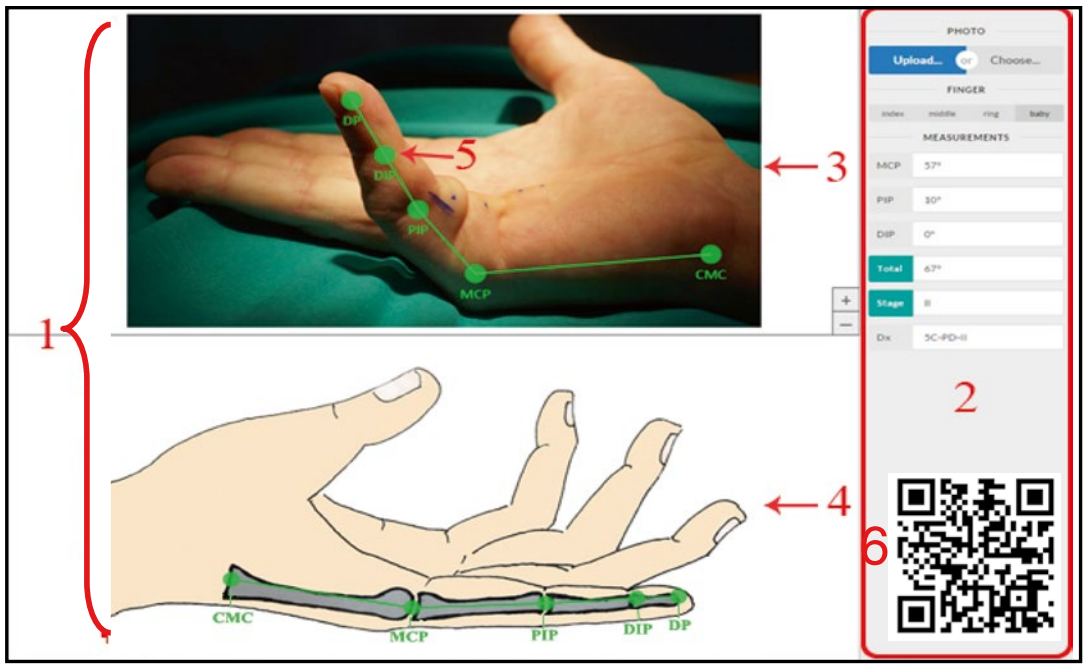

Fig. 31.1 User interface for determining the degree of Dupuytren contracture by photography. *1* working zone, *2* primary zone, *3* uploaded photo, *4* diagram with an example where to place marks, *5* green markers after correct placing, *6* QR code for link to application (http://dupuytren.medesse.com)

31.4.1 Reproducibility of Measurements

The goal of this test was assessing measurement errors and finding the optimal position points for the markers to minimize measurement errors. Before starting the test, the extension deficits of a little finger were identified using a standard goniometer. Then the picture of the hand was taken by a digital camera and was loaded into the application. 10 volunteers, previously not familiar with the software, were shortly introduced to it and were then asked to measure the degree of Dupuytren contracture using the application with the same picture. They were given two tasks: first, to place the markers on the picture in the center of the finger joints as indicated in the example at the bottom (Fig. 31.1) and, second, to place them on the edges of the finger, at the joints projection and as close to the finger as possible (Fig. 31.2).

Results of this measurement series are summarized below in Table 31.1.

Results show that placing dots on the edge gives less measurement errors. When placing the measurement dots on the edge of the finger, the errors did not exceed 3°, while by placement at the middle of the finger, errors amounted to up to 10°. Furthermore we can conclude that the software was intuitive to all users.

31.4.2 Influence of the Camera Angle

The same users as in 3.1 were then asked to measure the angles of the same finger but now using pictures that were taken at various angles. As standard, we took a picture made in exactly lateral projection with the position of the hand relative to the horizon lens at 180°. Other pictures were taken at 170°, 160°, 150°, 140°, and 130° angles. Results show that correct determination of Dupuytren contracture is possible on the pictures taken at 170–150°. On the photographs made at angles of 140°, 130°, and lower, the degree of Dupuytren contracture was determined with great difficulty. Thus, it may be concluded that for our software, we best use pictures taken in the range from 180° to 150° relative to the

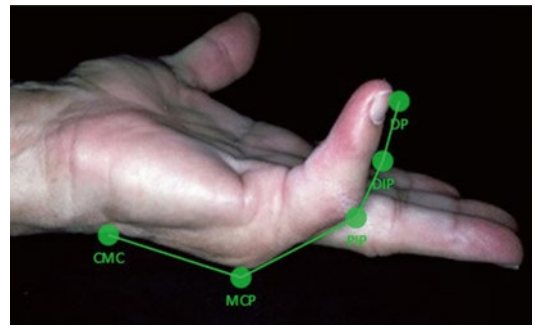

Fig. 31.2 Alternative placement of measurement markers at the edge of the finger

Table 31.1 Results of the reproducibility test

Joint	MCP joint		PIP joint		DIP joint		Summary		Code of the disease
Goniometer	45°		45°		0°		90°		5C-PD-III
No of tester	Center	Edge	Center	Edge	Center	Edge	Center	Edge	
1	48°	46°	41°	44°	1°	0°	90°	90°	5C-PD-III
2	41°	43°	57°	48°	−7°	−2°	91°	91°	5C-PD-III
3	41°	42°	50°	45°	−6°	−1°	91°	87°	5C-PD-II
4	43°	45°	35°	44°	2°	−3°	80°	89°	5C-PD-III
5	42°	45°	20°	45°	16°	−1°	70°	90°	5C-PD-III
6	55°	44°	45°	40°	4°	5°	100°	90°	5C-PD-III
7	58°	48°	35°	42°	1°	2°	94°	92°	5C-PD-III
8	32°	43°	40°	45°	−7°	−3°	72°	88°	5C-PD-II
9	65°	44°	20°	47°	6°	−3°	91°	91°	5C-PD-III
10	41°	43°	25°	45°	13°	1°	79°	89°	5C-PD-III

horizon lens. In other words, the tilting of the hand should not exceed 30°.

Conclusion

The software presented here allows objectifying and standardizing the processing of pictures taken before and after the operation and can become an alternative to measuring angles by a protractor (Smith et al 2009; Otter et al. 2015). Additionally, this program is very easy to handle and allows a patient to reliably measure the degree of contracture/extension deficit by himself, if the software is available to him, or in uploading the picture online to the clinic (Gheorghiu and Bhalaik 2015; Jahns 2010; Krause et al. 2015).

Conflict of Interest Declaration None to declare.

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Part VII

Comparative Studies and Economics

Bert Reichert and Tim Davis

Treatment of Dupuytren Disease: Where Are We Now?

32

David Elliot

Contents

32.1 Introduction

In treating Dupuytren Disease, we have too many options and, while every choice avoids complications, each risks others. So, we repeatedly have to balance their relative merits.

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32.2 Early History

Starting at the beginning, John Hueston was very keen on the Viking theory, with spread of the disease through Europe by the Vikings between 600 and 1000 AD.

> …. it is not unreasonable to term this the 'Viking disease'. (Hueston 1987)

The Vikings colonised northwest Scotland where Dupuytren Disease is certainly very common generally, not just among players of the bagpipes, who call it the 'Cruimein', or 'Crooked', curse, as it stops them playing their instrument. The Vikings then sailed in every direction, including to Iceland. There are suggestions that primitive hand surgery might have been performed by holy men in the northern isles, particularly by Bishop Thorlakur, trained in the monasteries of middle Europe, which were the hospitals of the time. One recorded instance could have been the first fasciotomy for Dupuytren Disease, despite interpretation later by a scribe as a miracle cure, although this could have been several chronic trigger fingers!

> There was a man called Borhallr, poor, disabled and old.
> He had a hand in which the fingers were clenched into the palm……
> Then he raised up anew his petition to Bishop Thorlakur.
> …… awoke in the morning completely healed.
> The fingers were straight and supple, easy to flex and straighten and there was strength in the hand. (Whaley and Elliot 1993)

The main concern about this theory is that there is no mention of the disease in the extensive mediaeval medical literature (Elliot 1988a, 1988b, 1989, 1999), by which time it should have been fairly common. Skoog (1948), the authority on this condition of his time, commented that 'There are no definite statements available regarding race incidence'. The theory may have developed from an innocent suggestion by Early in Manchester in the 1960s:

> ….. If one postulates the condition as having arisen in one particular racial group (the Nordic for example) then the variable distribution in other parts of the world might be explained on the basis of such a migration. (Early 1962)

32.3 Seventeenth and Early Eighteenth Centuries

By the late 1700s, this disease, known as 'crispatura tendinum', was clearly being recognised by European surgeons. Believed to be a contracture of the flexor tendon, it was considered inoperable.

32.4 Splinting as a Primary Treatment

Baron Boyer, in Paris, in the eleventh volume of his massive text of surgery, still referring to crispatura tendinum, advised never to divide the flexor tendon but that splinting will slow the disease:

> … a wise surgeon would be wise always to abstain [from operating to divide the tendon] ……one can perhaps stop the progress of the disease in its early stages by placing on the dorsum of the finger a small splint fixed with bandages…. (Boyer 1826)

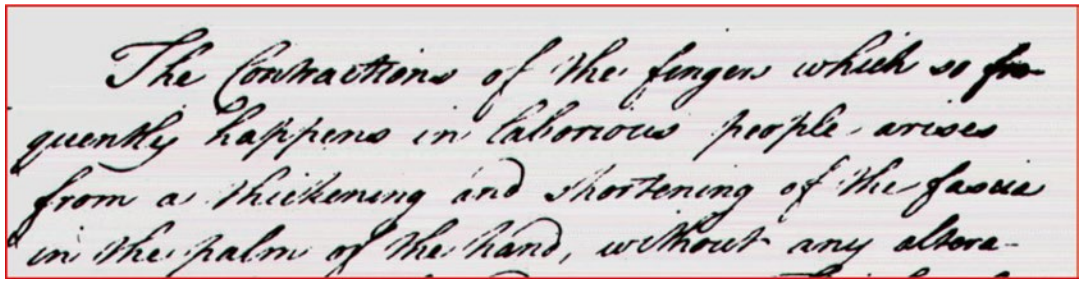
Night splinting to slow disease progression may still be preferred to more active treatment, especially for the PIP of the little finger, particularly in the elderly and, sometimes, in the not so elderly if our previous treatmsents are failing or disease reappears.

32.5 Recognition of the Pathology of the Disease and the Introduction of Fasciotomy

However, before the end of this century, the true pathology had been recognised, and surgeons were dividing the Dupuytren cords in the palm.

Without anaesthetic, antisepsis or antibiotics, they needed a quick operation. Cline and Cooper were operating through tiny skin incisions, intended to keep infection out (Cline 1787, 1808). Cooper, in 1822, warned that this was only safe in the palm, which is still true today. The 'bistoury', or scalpel, of the time, had a blade as small as a hypodermic needle, so percutaneous needle fasciotomy is not a new procedure!

Dupuytren (1831) and Caesar Hawkins in London (1844), shortly after, preferred large inci-


The Contractions of the fingers which so frequently happens in laborious people arises from a thickening and shortening of the fascia in the palm of the hand, without any ulcera-

sions left open to let pus out, with Dupuytren being the first surgeon to use the 'open-palm' technique, albeit for a different reason to that of later enthusiasts of this technique.

> (Cline 1777)
>
> It does not appear that Dupuytren met with any mischief when he did the operation in this way…….. I think it would be altogether impossible to escape suppuration in some of the several incisions. (Hawkins 1844)

32.6 Segmental Fasciectomy

Goyrand introduced the first elaboration by removing short segments of the disease to reduce the chance of the divided ends reattaching, and 'segmental fasciectomy' came into being (Goyrand 1833, 1835). Still a quick operation which the author does routinely, instead of fasciotomies, in the elderly, as it is still possible to perform under local anaesthetic and a tourniquet, with, arguably, a lower recurrence rate. Tourniquet time, of course, ceases to be an issue if one uses local anaesthetic with adrenaline.

32.7 The Advent of General Anaesthesia (1846)

Fasciotomy (aponeurotomy) or segmental fasciectomy (aponeurectomy) was the state of play in 1839 (Bougery and Jacob 1839). The year 1846 saw a quantum leap in all surgery. Within months of the use of general anaesthesia by Messrs, Clarke, Long and then Morton in Boston, USA, the whole of America and Europe were doing all varieties of surgery never possible previously. First in our field was William Fergusson, of King's College Hospital, London: with all the time in the world, he did a complete finger fasciectomy, still our commonest operation today.

> An incision should be made lengthwise over the whole of the contraction,
> and, if the integument [skin] be tolerably soft and thick, it should be turned off on each side, so as to expose the fibrous tissue, which should then be carefully taken away. (Fergusson 1846)

There was an unpredicted twist in the tail of Fergusson's operation. The previous small operations had been carried out through multiple incisions with skin bridges between them, while this new operation made a cut the full length of the finger, risking healing with a scar contracture. Fergusson solved the problem by making several horizontal skin cuts and allowed these to heal by secondary intention under dressings. Three further ways of avoiding scar contractures were to be created later in the nineteenth century, namely, zigzag incisions, z-plasties and skin grafting with full-thickness and split-thickness skin, and all are still used to avoid this problem after opening the skin on the palmar surface of the digits.

32.8 Operating Under Skin Bridges

The long Fergusson incisions can be avoided by making transverse incisions and removing the Dupuytren Disease under skin bridges. McIndoe taught this in the 1950s and Burkhalter used the technique more recently. McCash (1964) used the McIndoe approach and then moved the skin bridges distally to close all the skin openings

except that of the palmar wound. In the 1970s, these techniques were largely abandoned after strong criticism by Tubiana and others because of the risk of dividing nerves: the first point of nerve danger during fasciectomy being in the distal palm when the neurovascular bundle is pulled centrally by a spiral band, directly under the first of McIndoe's skin bridges. The Fergusson approach is much safer.

32.9 Late Nineteenth Century

By the end of the nineteenth century, Fergusson fasciectomy in operating theatre conditions more like today was the European 'norm', with one exception. William Adams, in London, the doyen of Dupuytren surgery and the most prolific writer on the subject from 1860 to 1900, was still performing Cline-Cooper fasciotomies through very small skin incisions (Adams 1879, 1892) and had worked out how to do this in the fingers without cutting the digital nerves, a technique drawn to our attention again recently by Short and Watson (1982) and then Foucher et al. (2001), but not something for the occasional practitioner! For most of us, percutaneous fasciotomy remains a palm-only technique and only on cases with simple, raised, pretendinous bands, not the 'sheet' disease which involves much, or the whole, of the palm, tethering and distorting the palmar skin considerably.

32.10 The Background of Anaesthesia and Surgery in the Nineteenth Century

Below is the background of technical changes in limb anaesthesia and surgery in the nineteenth century, against which these changes in Dupuytren surgery were evolving.

1807 Ice local anaesthesia (Larrey)
1842 Ether general anaesthesia (Clarke)
1844 Hypodermic needle (Rynd)
1853 Syringe (Wood)
1863 Micro-organisms demonstrated (Pasteur)
1863 Carbolic antisepsis (Lister)
1864 Exsanguination by elevation (Lister)
1866 Ethyl chloride spray (Richardson)
1871 Exsanguination by rubber bandage (Grandero-Sylvestin)
1873 Exsanguination by rubber bandage (von Esmarch)
1884 Cocaine local anaesthesia (Halsted & Hall)
1886 Heat Sterilisation (von Bergman)
1890 Rubber Gloves (Halsted)
1904 Exsanguination by pneumatic tourniquet (Cushing)
1908 Intravenous anaesthesia (Bier)

32.11 Postoperative Splinting

As early as 1831, Dupuytren was advocating postoperative splinting, whether to avoid reattachment of cut ends of the Dupuytren cord after fasciotomy or simply to stretch the scar filling this gap.

> le 12 de juin 1831 – Opération 1 : M. L.... Marchand de vins en gros..... . le 14 – au matin, on substitute une machine, plus habilement confectionnée par Lacroix (Bandagiste)
> le 5 décembre 1831- Opération 2: On doit employer sur ce malade la machine imaginée par Lacroix. (Dupuytren 1831)

Adams (1892), using more sophisticated splints made of metal covered by leather than our thermoplastic ones, was aware that subcutaneous scar contracture from the surgery could spoil the result. He also knew that surgical scar could be stretched by splints and only contracted for 4–6 months. So night splinting for this period would maintain his operative gain. This is the author's current reason for night splinting after surgery.

32.12 Stretching Dupuytren Disease

Only much more recently have we realised that Dupuytren cords can also be stretched. In 1831, Dupuytren considered this possibility:

> …… on more than one occasion, we have seen that a weight of 100, and even 150, livres [489.5 g] could be hung from the hook formed by the finger, without its angle of flexion straightening at all. (Dupuytren 1831)

However, it was not until 1968 that this became a reality with a brief report in the Russian literature by Chamraev (Chamraev 1968; Sirotakova and Elliot 1997). Later, the technique was considerably refined by the Messina family (1991, 1993, 2016).

32.13 Dermofasciectomy

Going back a little in history again, dermofasciectomy, that is removing the overlying skin with the disease and then replacing it with skin graft, was described by Lexer (1931) and popularised in the 1950s and 1960s by Hueston and Iselin, Hueston using full-thickness skin graft and Iselin using split-skin graft. There is no difference in the functional results between the two grafts (Iselin 1986). Even the heaviest manual labourers will only occasionally wear through a graft. Although disease reappears much more rarely after dermofasciectomy (Hueston 1984a), with reappearance in the same digit being less than 10% at 10 years, this procedure is only done reluctantly by most surgeons as it is perceived as a bit too much surgery, probably for both the patient and the surgeons, and there is a worry about possible graft failure, although this is actually not common. So dermofasciectomy is only performed in the UK when reappearance is particularly likely, in other words in repeatedly reappearing disease or in cases which manifest before the age of 40 years old. This latter indication is tending to be forgotten at present, although John Hueston, in the 1960s, clearly identified a 92% reappearance rate within 2 years after skin-preserving operations in this age group (Hueston 1963).

32.14 Fibre-Break Grafting

Even Hueston was looking for an alternative to this large operation when he described his 'fire-break' technique of putting in smaller grafts (Hueston 1984b), so that any disease reappearance cannot travel up the finger, contract and flex the finger, and require reoperation. He later changed the name to 'fibre-break' grafting, as he realised that Europeans did not suffer the bush fires of his native Australia. Unfortunately, he died before he could prove the idea. We have operated on over 300 hands with Dupuytren Disease in this way since 1994 and are looking at the 10-year follow-ups. In the first 80 previously operated fingers, collected at 5 years, we had reoperated on only eight fingers for disease causing contracture, although recurrence between the grafts is more common than the need to reoperate.

Recurrence only occurs in the distal palm and in the middle phalanx, never in the proximal palm, making a palmar 'fibre-break' graft unnecessary, and we now only graft the proximal 50–75% of the proximal phalanx. While failure of grafting is unusual, over and above the increased operation time, I think there is one caveat to this procedure. Starting to mobilise the hand after a seven day delay, while the grafts take, worsens the tendency to postop stiffness of the hand. In his classic paper of 1964 on the 'open-palm' technique, although not the main point of the paper, this was noted by McCash as a disadvantage of grafting, with the open palm having the benefit of allowing early escape of oedema.

32.15 The Open-Palm Technique

Historically, the open-palm technique has been advocated on three occasions for three different reasons. Dupuytren (1831) was the first to use the open palm, to allow escape of pus, described at that time as 'inevitable' and, in an era of surgery without antisepsis or antibiotics, liable to lead to loss of the limb or, even, life if not liberated quickly. McCash subsequently (1964) advocated the technique to avoid palmar haematoma after complete removal of the palmar fascia, which was the routine operation of his time. He believed this created a dead space in the palm and a risk of haematoma collection, certainly a complication to avoid as this almost always leads to a very stiff hand and poor result of surgery. Two outstanding surgeons of our time have commented to the author on McCash's logic, or the lack of it. Richard Smith in Boston asked the question why

leave the wound open when the rest of the surgical world avoided this problem with drains, even in McCash's time. Dieter Buck Gramcko in Hamburg pointed out that McCash was wrong, there was no dead space after radical palmar fasciectomy and haematoma is rare. He routinely carried out a radical fasciectomy so the undiseased longitudinal palmar fibres cannot develop disease in the future, a logical thought process and a practice the author continues to use in many cases. Both diseased and undiseased longitudinal fibres of the ulnar three digits are removed. The palmar fibres of the index finger are underdeveloped and are rarely involved when disease affects this finger, so these fibres are left intact. This is an addition to any operation in which the palm is opened which may be of value as a prophylaxis and has a zero incidence of haematoma formation in our hands.

The terms 'radical' and 'limited' fasciectomies are confusing. Radical fasciectomy, meaning complete removal of the fascia in the palm, was almost routine in the 1950s. The term 'limited' fasciectomy was then added later to denote a removal of the fascia in the palm only of the fingers with disease, which is what is routine practice for most surgeons who advocate complete removal of any diseased tissue they can see in both the palm and fingers. This is a lesser operation in the palm. The term has remained, although we would currently perceive this operation as far from limited, and it would, perhaps, now be better called a 'ray' fasciectomy.

The third use of the open-palm technique, advocated by Gelberman et al (1982), was to reduce pain associated with closed suturing or grafting of the hand. This paper reports a very small number of cases with questionable results in terms of benefit of the open-palm technique. It is probably negated by the fact that most Dupuytren surgery is followed by little pain and is now routinely managed as day-case surgery requiring only simple analgesia postoperatively.

More recently, we described the use of the open-palm technique as one of a number of activities used to try to avoid a second episode of chronic regional pain syndrome type 1 in cases returning with further disease after a previous operation which was followed by this serious complication (Van Dam and Elliot 2014).

32.16 Amputation

Amputation for Dupuytren contracture, if the disease is severe and often recurrent, has been occasionally necessary but is NOT a good solution to the problem of a severe contracture that is unlikely to be relieved by surgery (or any other technique of treatment). A better alternative is to treat the palmar disease, using fasciectomy or alternatives, to straighten the metacarpophalangeal (MP) joint and, then, if the proximal interphalangeal joint will not straighten, to fuse this joint at a second operation using a dorsal approach. Another alternative is the Messina approach, straightening the finger by stretching the finger with dynamic traction and then removing the disease by fasciectomy, shortly after.

32.17 Reappearance of Disease in a Previously Operated Digit

It has been the generally accepted view for a good many years that the bigger the operation, the smaller the likelihood of reappearance of disease in that finger. Nevertheless, surgery, reporting reappearance of disease after fasciotomy in 50 % at two years and in 50 % at five years after limited fasciectomy, does not have an impressive rate of success. Long-term success in respect of reappearance of disease in an operated finger only reduces to 'respectable' with the much larger operation of dermofasciectomy. However, this operation is disliked by (even) experienced hand surgeons who are comfortable with skin grafting, probably largely because it increases the risk of creating sufficient oedema to give rise to a stiff hand.

This conference was conceived to consider the alternatives to the above.

32.18 Steroid

Steroid can work on nodules but generally is believed to have no effect on cords of Dupuytren Disease, so is only useful for very early palmar disease. Ketchum and Donahue (2000) treated nodules in 75 hands in 63 patients over a four-year period in this way, with an average of 3.2 injec-

tions per nodule. Ninety-seven percent showed regression, some complete and 60–80 % incomplete. There was a 50 % recurrence of the nodules within 1–3 years.

32.19 Radiotherapy

Radiotherapy for Dupuytren Disease is being advocated by this profession and has been approved by NICE (2010), the body which approves treatments in the UK. It is claimed to be simple, safe and painless, being best in the early stages with minimal, or no contracture, so, again, only a treatment of early disease (Adamietz et al. 2001; Seegenschmiedt et al. 2012). It is said to be less effective with contractures of more than 10°. Peer-reviewed documentation of its value in terms of the problem which worries hand surgeons, namely, reappearance of disease in a treated digit, is lacking as it is a relatively 'new' treatment, at least with modern techniques of radiotherapy. The author has negative memories of the last time radiotherapy was used for this disease thirty years ago: the same complications occurred as brought this generation of plastic surgeons into breast cancer surgery, namely, acute skin necrosis and delayed skin necrosis from radiation vascular damage. I am sure the current generation of radiotherapists will not 'burn' holes in the palm again, but the fact also remains that this treatment heals with fibrosis. Hand surgeons and their therapists spend a large amount of time trying to avoid scar deposition from oedema in the hand!

32.20 Fasciotomy and Needle Fasciotomy

Ten-year trialling needle fasciotomy tells us what we have known for one hundred years, namely, that the incidence of reappearance in treated digits is high, namely, 50 % at two years. This is not acceptable to the author's younger patients and the reason why fasciotomy was only used routinely in the elderly for much of the twentieth century (Colville 1983). In most hands, this is again only a treatment for early disease. However, the practice of needle fasciotomy is being changed by enthusiasts from a single, or perhaps two or three, fasciotomies to one of very many minor divisions of each cord along its entire length. In the hands of a skilled practitioner, it may not carry the risk of nerve division when performed in the fingers. The new technique may prove to take much longer than the outpatient needle fasciotomy as initially conceived. While the results of this newer activity will take several years to assess, it is an interesting development which may make this technique less disappointing than the reported results to date and also available for use in moderately severe contractures.

32.21 Collagenase

The use of collagenase is becoming increasingly popular as a way of avoiding surgery. Time will tell whether this is a fasciotomy or a segmental fasciectomy and whether the reappearance of disease in treated fingers accords with that of these surgical activities. Enthusiasts are using this technique in increasingly complex cases, but this, again, is mostly being used for relatively simple disease.

32.22 Chemotherapy

Systemic chemotherapy has been perceived as too dangerous for use in this disease, which is mostly a nuisance to the patient and certainly not life-threatening. However, perhaps hand surgery should consider the enormous success of systemic chemotherapy, especially methotrexate, in virtually eliminating rheumatoid hand pathology from the experience of most younger hand surgeons. Systemic chemotherapy is now also being used to treat many other medical conditions which are largely an inconvenience and not life-threatening. Local chemotherapy is the dream of all of us. A recent paper by Degreef et al. (2014) describing the use of high-dose tamoxifen as a neoadjuvant treatment in minimally invasive surgery for Dupuytren Disease in patients with a strong predisposition towards fibrosis suggests that something useful may come of pursuing this dream.

32.23 Choosing a Treatment

Unfortunately, all of these alternatives to surgery are only of any use if disease is seen early or relatively early. A recurrence at two years is rarely convenient to younger patients and can also be inappropriate in the elderly. So, we need to know the rate of reappearance of disease following all of these treatments before 'selling' them too strongly.

32.24 Surgical Training

It needs also to be remembered that young surgeons need to be trained in the surgical techniques of fasciectomy as this painless condition not infrequently still presents as advanced disease. It also does not always respond to our primary treatment, and recurrence is often more difficult to treat by any other modality than surgery than primary disease, however, treated initially. Cases requiring difficult and lengthy surgery will continue to present.

32.25 Early Intervention: An Imperative

We can only try to move away from difficult and lengthy surgery, with its operative risks and postoperative complications, to the alternatives described above, if we see this disease earlier AND treat it earlier. Seeing the patients earlier is not so easy when this is a painless condition, although the author believes that more patients are presenting earlier, as they are doing with many other conditions. Prophylaxis is perhaps the greatest medical success of our time and patients, particularly the younger ones, with Dupuytren Disease mostly do not tolerate even the early distortion of the hand caused by this disease, or fear treatment, as they did in earlier times.

In the UK, there are still many surgeons, as well as family doctors, sending patients away until the disease is causing significant finger contracture, telling them that the problem only merits surgery once the finger is bent in. John Hueston invented his 'table-top' test (Hueston 1976) to stop patients presenting with several fingers, often of both hands, with an advanced degree of contracture(s). It was appropriate to the era in which it was described. Unfortunately, it still is being used to identify the appropriate time to seek surgical (or other) treatment. This disease usually starts in the palm and comes on over months to years. Typically, it forms a nodule around the level of the palmar crease, grows proximally towards the carpal tunnel, ceases to progress in this direction and finally grows distally. As it does so, it crosses the distal palmar crease, marking progress across the MP joint(s). We, and the patients, then have the opportunity to observe a slow loss of hyperextension of the MP joint(s). Once this starts, progress into the finger is usual, the only variable being the timing of this progress. We can measure this sequentially by recording the distance between the corner of the nail bed of an affected digit and the table top (Van Dam and Elliot 2014). As the loss of hyperextension progresses, there is little doubt where the cord is going! If treated, surgically or otherwise, before the finger cannot be lifted off the table, this only requires a small procedure. Even surgery does not open the finger but remains a palmar fasciectomy and requires no postop therapy or splinting: it is the opening of the proximal phalangeal segment of the finger which precipitates the oedema problem requiring postoperative treatment.

Conclusion

Whatever modality of treatment is used, we must be prepared to treat early and the author was greatly encouraged to see many practitioners at this conference using techniques that drive management down this path. Late surgery, not surgery per se, is too often a purveyor of bad long-term hand function and needs to be avoided whenever possible.

Conflict of Interest Declaration The author has no conflict of interest to declare.

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Steroid Injection and Needle Aponeurotomy for Dupuytren Disease

33

Catherine McMillan and Paul Binhammer

Contents

33.1 Introduction

In the absence of a cure for Dupuytren Disease (DD), the hand surgeon's role in management is to correct joint contractures and restore function. Needle aponeurotomy (NA) is one of many treatment options for contractures caused by DD. Because NA is associated with a brief recovery period, low incidence of complications, and low cost, it represents an attractive option to patients who desire convenience and to those unable to undergo more invasive treatments due to age and/or coexisting conditions (Diaz and Curtin 2014). NA is also suitable for the treatment of recurrence in DD (van Rijssen and Werker 2012). Although NA is a viable treatment option for most patients with DD and this procedure is widely performed, its reported recurrence rate, which ranges between 33 and 100 %, appears to be higher than those of fasciectomy (Werker et al. 2012) and clostridial collagenase injection (Peimer et al. 2015; Zhou et al. 2015).

A potential role for steroid injections in the treatment of Dupuytren nodules has been suggested through both clinical and molecular studies (Ketchum and Donahue 2000; Meek et al. 1999, 2002). The mechanisms through which steroids may provide a benefit have been reported to include a decrease in fibroblast proliferation and an increase in apoptosis of both fibroblasts and inflammatory cells (Meek et al. 2002; O'Gorman et al. 2010). In the literature, injection of the corticosteroid triamcinolone acetonide (TA) into keloids and hypertrophic scars has resulted in positive outcomes (Perdanasari et al. 2015). One group reported at least 50 % resolution after 1 or more intralesional injections (Ketchum et al. 1971). This group later demonstrated a modification in disease progression after serial injections of TA directly into Dupuytren nodules (Ketchum and Donahue 2000). These findings suggest a potential

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role for TA in the treatment of DD. The potential benefit of steroid injections in patients with palpable cords and joint contracture caused by DD, however, remains unclear (Sood et al. 2015).

The high incidence of recurrence associated with NA warrants investigation into the potential benefit of treatment adjuncts. It may be possible for steroid injections to enhance and prolong the mechanical benefits of NA by modifying the cellular microenvironment of the palmar fascia. The objective of this randomized controlled study was to compare outcomes associated with a combination of serial TA injections and NA (NATI group) versus NA alone (NA group) in patients with DD. The primary outcome was total active extension deficit (TAED) at 6 weeks, 3 months, and 6 months. Secondary objectives were to examine re-treatment rates and evaluate the significance of baseline factors on time to re-treatment up to 48 months.

33.2 Methods

33.2.1 Study Design and Participants

All study procedures were reviewed and approved by the institutional Research Ethics Board. An open-label randomized controlled design was utilized to prospectively determine the impact of steroid injections combined with NA on joint contracture at follow-up points 6 weeks, 3 months, and 6 months. Participants were instructed to follow up as needed after 6 months. Those not returning within 18 months were asked to attend a follow-up assessment. Joint contractures (TAED) and the percentage of correction maintained from baseline were recorded at follow-up visits. The timing and details of re-treatment, which was patient driven, were recorded. Study participation began at the time of the initial NA and ended once a patient received re-treatment.

A pre-study power calculation performed to determine the appropriate sample size for this study indicated that 18 subjects per group would provide 81 % power using an alpha of 0.05. The target number for recruitment was therefore 44 subjects after presuming an anticipated drop-out rate of 15 %.

Study inclusion criteria included a diagnosis of true DD by the senior author (PB) and at least one joint contracture of at least 20°. Consecutive patients were invited to participate in the study with the exception of those with diabetes mellitus and those who had previously undergone hand surgery for any condition or trauma. In cases of bilateral disease, data pertaining to only the hand being treated first, which was patient driven, was included in the study.

33.2.2 Procedures

Informed consent was obtained after confirmation of eligibility through consultation. On a separate day immediately before the procedure, a research assistant randomized participants via electronic random number generator to either the NATI group or the NA group and informed subjects of the study group to which they were randomized. Joint contractures at all time points were measured using the same goniometer by the senior author.

Immediately prior to the procedure, baseline joint contractures were recorded in degrees, and TAED was represented by the sum of all contractures. Subjects randomized to the NA group received NA only, and those randomized to the NATI group underwent NA followed immediately by an injection of TA into the released cord. Follow-up injections were administered at 6 weeks and 3 months for NATI subjects with areas of palpable thickness along previously released cords. The senior author performed all procedures and administered all TA injections.

Under local anesthesia using 1 % lidocaine and alcohol skin preparation, cords were percutaneously divided, using the bevel of a 16-gauge injection needle. Local anesthesia was restricted to the skin and a digital nerve block was avoided so that any contact between the releasing needle and the neurovascular bundle could be identified. Multiple points of division were performed along cords. The procedure was terminated when the finger could be passively straightened to an

extended posture, to a TAED of 0°. If the digit could not be straightened, further points of release were performed until the digit could be straightened or it was felt that no more points could be released. Supplemental digital block was performed at this point using a long-acting local anesthetic to provide postoperative anesthesia. Small dressings were applied and usually discontinued within 48 h. Medications were not prescribed. Patients were subsequently fitted with a custom thermoplastic orthosis and were directed to wear it at night for 3 months to maintain digital extension. A daily stretching program was advised for the first 6 weeks to maintain range of motion. Compliance with splinting and stretching instructions was not recorded.

Following NA, participants in the NATI group received a TA injection directly into the treated cord(s) using a 25-gauge needle. Injections were administered between points of release, with the dose of TA split between points. Dosing estimates of the preparation TA injectable suspension USP (40 mg/ml; Sandoz Canada Inc., Boucherville, Quebec) were based on published guidelines developed for the treatment of hypertrophic scars and keloids and Dupuytren nodules (Ketchum and Donahue 2000; Chowdri et al. 1999). Based on the extent of the disease, a range of 8–48 mg TA was injected per digit to a maximum of 120 mg per hand to avoid untoward systemic effects. The volume of TA suspension leaking out through puncture sites caused by the NA was not measured.

33.2.3 Follow-Up

All participants were asked to return for follow-up assessment at 6 weeks, 3 months, and 6 months and as needed thereafter. TAED was measured in all participants at all follow-up time points, and complications were recorded. Subjects in the NATI group with areas of palpable thickness at 6 weeks and 3 months received follow-up injections of TA into these areas. The dose of TA, which was estimated based on residual cord size, was divided between injection sites. Follow-up injections were not administered after the 3-month follow-up. Newly developed cords were not injected.

After 6 months, participants were instructed to return for follow-up as needed. Patients who had not returned within 18 months were asked to attend a follow-up assessment. After 3 attempts without response, a subject's data was excluded from long-term follow-up analyses. TAED was measured at each follow-up and the timing of re-treatment and procedural details were recorded. Re-treatment was defined as a second procedure to treat at least one of the digits treated at baseline. The provision of re-treatment was patient driven.

33.2.4 Analysis

A repeated-measures analysis of variance was performed to determine differences between the NATI and NA groups, time points, and interaction between group and time. Independent two-sided t-tests were performed to assess for significant differences between TAED at 6 weeks, 3 months, and 6 months. Baseline characteristics were compared using t-tests for continuous variables and the Fisher exact test for categorical variables.

Mean TAED was calculated to summarize the time periods of 7–12 months, 13–24 months, 25–36 months, and 37–48 months. While the objective was to follow the sample for 48 months, data up to 53 months was included because it was available. Measurements after 48 months were compared wherever possible. If a participant returned for follow-up more than once during the same 12-month period, only the most recent TAED was used to calculate the group mean for that period. The study ended for a participant once re-treatment was performed. The TAED measured immediately before re-treatment was included in data analysis.

Kaplan-Meier survival analysis was used to estimate the percentage of participants undergoing re-treatment as a function of time. Log-rank tests were used to compare the percentage of patients in each group expected to undergo re-treatment within 24 months, 36 months, and

48 months. Treatment group, sex, baseline age, baseline TAED, and number of digits and joints treated at the original NA were considered in a stepwise proportional hazards regression. Follow-up TAED measurements prior to re-treatment were included as a time-varying covariate to determine the degree to which follow-up TAED was associated with earlier re-treatment.

33.3 Results

Fifty-one patients agreed to participate in the study. Three subjects discontinued within the first 6 months due to geographical location and one subject refused follow-up TA injections. The final sample size for the 6-month analysis was 47, including 23 in the NA group and 24 in the NATI group. A summary of baseline characteristics is presented in Table 33.1. Groups did not differ significantly for any baseline characteristic, or for TAED. Participants were completely healed by the 6-week follow-up. No subjects in either study group presented with infection, reported altered sensation within digits after the procedure, or reported any other side effects or complications.

There were no significant differences between groups when comparing baseline mean TAED, which was 80 (±45) degrees in NA participants and 103 (±76) degrees in NATI participants ($P = .21$). The number of affected MCP joints and affected PIP joints did not differ significantly between groups. The mean number of affected MCP joints and the mean number of affected PIP joints in each group did not differ significantly ($P = .11$; $P = .52$, respectively). Baseline TAED of MCP joints did not differ between groups and baseline TAED of only PIP joints did not differ between groups ($P = .16$; $P = .73$, respectively). A more extensive presentation of the study sample at baseline is presented in McMillan and Binhammer (2012).

The volume of TA injections and the number of cords injected at each time point are shown in Table 33.2. Dose of TA and correction percentage were not correlated.

The average number of days between the procedure and follow-up assessments did not differ significantly between groups, with the exception of the subjects in the NA group returning for the 3-month follow-up significantly later than the NATI group ($p < .01$).

A repeated-measures analysis of variance failed to detect a significant group by time interaction ($P = 0.11$), indicating similar trends in each group over time. A significant time effect indicated that TAED decreased significantly over time in both groups ($P < .001$), indicating effective treatment in both groups. Additional analyses of the 6-month data have been published previously (McMillan and Binhammer 2012).

After the 6-month follow-up assessment, 44 participants returned for reexamination an average of 4.8 times during the follow-up period, which ranged from 7 months to 53 months after the original NA. Three subjects could not be contacted after the 6-month follow-up point and could not be included in long-term follow-up analyses.

Table 33.1 Baseline characteristics of participants

–	NA subjects ($N = 23$)	NATI subjects ($N = 24$)	All subjects ($N = 47$)	P value
Age	60.5 ± 10	62 ± 8	61 ± 9	.64
Male	19	22	41	.42
Joints	40	57	97	.12
Digits	29	38	67	.31

Plus-minus values represent standard deviation (SD)

Table 33.2 Number of cords receiving TA injections and mean dose per subject at each time point

–	After procedure	6 weeks	3 months	6 months
N (number of subjects)	24	24	24	0
Total cords injected	38	37	29	0
Mean dose/subject (mg)	42	34	24	n/a
Dosage range (mg)	16–120	12–100	0–80	n/a

Table 33.3 Means of (a) follow-up in months, (b) TAED in degrees, (c) mean percentage correction, and re-treatment rates in each study group

Time point/period	NA group	NATI group	*P* value
Baseline (*N*)	23	24	–
(a) Follow-up	n/a	n/a	–
(b) TAED	80 ± 45	103 ± 76	.21
(c) % correction	n/a	n/a	–
(d) re-treatments (*N*)	n/a	n/a	–
6 weeks (*N*)	23	24	–
(a) Follow-up	1.5 ± .3	1.4 ± .1	.23
(b) TAED	19 ± 14	17 ± 18	.68
(c) % correction	74	87	**.02**
(d) re-treatments (*N*)	0	0	–
3 months (N)	23	24	–
(a) Follow-up	3.5 ± .8	3 ± .2	**.003**
(b) TAED	16 ± 15	15 ± 17	.84
(c) % correction	76	88	**.05**
(d) re-treatments (*N*)	0	0	–
6 months (*N*)	23	24	–
(a) Follow-up	6.5 ± .7	6.5 ± 1	1.0
(b) TAED	26 ± 21	15 ± 18	.08
(c) % correction	64	87	**.003**
(d) re-treatments (*N*)	0	0	–
7–12 months (*N*)	4	7	–
(a) Follow-up	9.5 ± 3	11 ± 2	.2
(b) TAED	34 ± 5	16 ± 24	.4
(c) % correction	56	88	**.02**
(d) re-treatments (*N*)	2	0	–
13–24 months (*N*)	8	12	–
(a) Follow-up	19 ± 5	18 ± 5	.8
(b) TAED	70 ± 31	27 ± 25	**.003**
(c) % correction	16	72	**.01**
(d) re-treatments (*N*)	4	1	–
25–36 months (*N*)	9	8	–
(a) Follow-up	32 ± 4	30 ± 4	.8
(b) TAED	62 ± 21	47 ± 56	.45
(c) % correction	28	70	**.002**
(d) re-treatments (*N*)	2	3	–
37–48 months (N)	7[a]	7[b]	–
(a) Follow-up	42 ± 2	42 ± 3	.7
(b) TAED	63 ± 33	52 ± 75	.75
(c) % correction	−5	65	**.04**
(d) re-treatments (*N*)	4	3	–
49–53 months (*N*)	4	2	–
(a) Follow-up	50 ± 2	50 ± .3	n/a
(b) TAED	52 ± 26	34 ± 33	n/a
(c) % correction	9	67	n/a
(d) re-treatments (*N*)	1	0	–

Plus-minus values denote standard deviations. Bolded font indicates statistical significance

[a]TAED value missing for 2 participants

[b]TAED value missing for one participant

Table 33.3 compares study groups at all time points up to 6 months and each subsequent 12-month period in terms of TAED, percentage correction from baseline, and re-treatment. For the 47 subjects, mean TAED did not differ at baseline, 6 weeks, 3 months, or 6 months. Results of an analysis including only the follow-up sample (44 participants) between 7 and 53 months have been published separately (McMillan and Binhammer 2014).

When excluding the three participants who did not return for at least one post-6-month follow-up, TAED at 6-months was significantly lower in NATI group subjects (21 NA group subjects, 23 NATI group subjects; $P = .009$). Mean TAED of subjects returning between 13 months and 24 months was also significantly lower for the NATI group. Mean TAED did not differ significantly between groups during the 24–36-month and 37–48-month periods. Mean percentage correction from baseline was significantly higher in the NATI group at all time points in the first 6 months and for each subsequent 12-month period. An insufficient number of follow-up assessments precluded analysis of the 12-month period beyond 48 months.

Thirteen NA group participants and 7 NATI group participants returned for re-treatment within 53 months of the original NA procedure. All re-treatments were performed on contractures treated at baseline. All 7 NATI group subjects underwent NA as the procedure for re-treatment. In the NA group, 3 subjects underwent fasciectomy and 10 underwent a second NA procedure. The mean time between the original NA procedure and re-treatment for the NA group (29 months) did not differ significantly from that

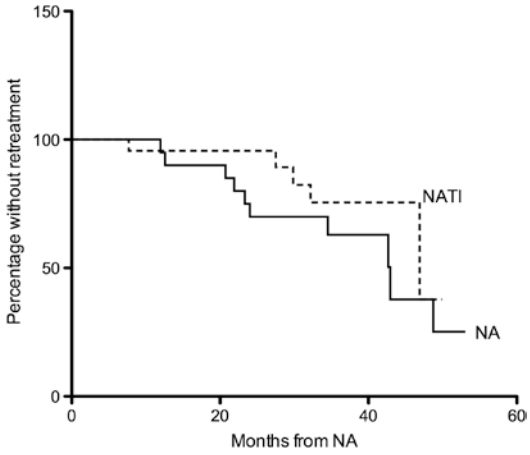

Fig. 33.1 Kaplan-Meier survival curves showing the percentage of subjects in each group expected not to receive re-treatment plotted against months from NA

of the NATI group (34 months; $P = .07$). Mean TAED immediately prior to re-treatment was 104° in the NATI group and 84° in the NA group, which was not statistically significant ($P = .3$).

Kaplan-Meier survival estimates based on follow-up data collected between 7 and 48 months indicated that a smaller percentage of NATI group subjects were expected to return for re-treatment compared with NA group subjects at 12, 24, and 36 months (Fig. 33.1). This difference was statistically significant at 24 months only ($P = .05$). By approximately 48 months, groups did not appear to differ. The log-rank test indicated a tendency, although not significant, for NA group subjects to return for re-treatment before NATI group subjects ($P = .27$).

Regardless of study group assignment, participants with 2 or more baseline joint contractures and participants aged between 41 and 59 years at the time of NA tended to return for re-treatment significantly sooner than those with a single affected joint ($P = .02$), and older participants (60–65, ≥66; $P = .04$), respectively. No significant difference in time to re-treatment was detected between patients with one affected digit versus patients with 2 or more affected digits at baseline ($P = .5$). Baseline TAED did not significantly affect time to re-treatment ($P = .14$).

A stepwise proportional hazards regression analysis could not include sex as a variable as a result of too few female participants. Age and the number of affected joints at baseline were retained in a Cox proportional hazards model, which indicated that younger age and multiple affected joints were significantly associated with earlier re-treatment ($P = .009$, $P = .006$, respectively). When follow-up TAED measurements were analyzed as a time-varying covariate, only younger baseline age and higher follow-up (after the 6-months) TAED measurements were significantly associated with earlier re-treatment ($P = .003$, $P < .001$, respectively). The multivariate survival analysis indicated that only three factors were significantly associated with earlier re-treatment, which included baseline age (hazard ratio 0.93, $P = .009$), number of affected joints at baseline (hazard ratio 1.53, $P = .006$), and number of TAED assessments since baseline (hazard ratio 1.02, $P < .001$).

33.4 Discussion

Our results suggest that TA injections following NA may be associated with significantly less flexion deformity for up to 24 months compared with NA alone. The NATI group exhibited a trend of lower mean TAED than the NA group throughout follow-up. The largest increase (20°) in mean TAED in the NATI group occurred between 25 and 36 months, whereas the largest increase (36°) in mean TAED for the NA group occurred between 13 and 24 months. These findings suggest that TA injections may have contributed to extending the benefit of NA in this study by up to 12 months. This result is also supported by our data beyond 24 months, which showed that mean flexion deformity did not differ significantly between groups. In a study that evaluated outcomes in patients receiving TA injections into Dupuytren nodules, the authors found that disease reactivation had occurred in half of the subjects between 12 and 36 months after the last injection (Ketchum and Donahue 2000). Re-treatment within a similar timeframe was observed in this study for the NATI group. Injections to treat early DD, or more severe cases of DD with joint contracture, have not been adequately studied clinically, providing little evidence with which to compare and interpret these results (Sood et al. 2015).

Those receiving TA injections appeared to maintain a significantly greater percentage correction from baseline throughout follow-up than those receiving NA alone. Although a direct comparison of TAED was the primary outcome in this study, transforming the data to percentage correction enables a comparison that is relative to baseline contractures. Groups did not differ significantly for any baseline factor including TAED; however, TAED at the time of enrollment was 33° greater in NATI group subjects than in NA group subjects. The NATI group also presented with 9 more affected digits and 17 more affected joints than the NA group at baseline. While the severity of subjects in the NATI group appeared to be greater than NA group subjects, this difference was mostly attributed to the assignment of two individuals, each presenting with 6 severely contracted joints, to the NATI group. Therefore, preoperative variance may partially explain why comparisons of percentage correction in this study are statistically significant, while comparisons of mean TAED are not. It may be possible that the high percentage correction maintained in the NATI group is attributable to the greater potential for correction rather than due to the receipt of TA injections. This finding may also indicate that patients who tended to seek treatment for less severe disease largely comprised the NA group. The provision of re-treatment was likely dependent upon the flexion of previously treated joints and additional factors that were not included in our analysis. It is likely that patients with more severe contractures and/or those experiencing functional deficit during the follow-up period returned for reexamination earlier and more often than those with less functional deficit. Therefore, follow-up data collected after the first 6 months may provide a more accurate depiction of the most severe cases. As suggested by Broekstra and Werker (2012), matching enrolled participants based on risk profile may have prevented a possible selection bias.

Fewer NATI group subjects than NA group subjects returned for re-treatment by 53 months. In addition, our data revealed a difference in the timing of re-treatment between the two groups, with only one re-treatment in the NATI group occurring before 24 months, compared with six NA group re-treatments during the same period. Kaplan-Meier survival estimates indicated a significantly higher percentage of subjects in the NA group returning for re-treatment by 24 months than in the NATI group, supporting a possible protective role for TA injections. The percentage of participants in each group returning for re-treatment by 48 months was similar, implying a short-term delay to re-treatment in the NATI group.

Despite statistical comparisons and Kaplan-Meier survival estimates suggesting a potential role for TA injections in delaying re-treatment, multivariate survival analysis of our dataset showed that treatment group was not significantly associated with earlier re-treatment. Younger baseline age and the involvement of multiple joints were the only variables with a significant association to earlier re-treatment, which was observed regardless of study group assignment. An early age of onset of DD has been found in previous studies to predict increased risk of recurrence or progression (Hindocha et al. 2006; Reilly et al. 2005). It is not unexpected that patients with a greater number of joint contractures would return for earlier re-treatment, as they would possibly also be experiencing functional deficit. Notably, we did not find that subjects with higher baseline TAED or a greater number of affected digits to be predictive of earlier re-treatment.

This study was limited by a number of factors that may have influenced group comparisons. In addition to possible selection bias, patients were randomized before the NA procedure, introducing the possibility for investigator bias, as the same surgeon performed all procedures, injections, and measurements. The randomization of patients immediately following NA prior to TA injection and the use of a blinded evaluator could have decreased the likelihood of this bias.

The use of re-treatment as the study end point resulted in a steady decrease in the number of participants as re-treatments were performed. Implications of a decreasing sample size include difficulty interpreting and generalizing results. It may be possible that an adequately powered analysis would detect a significant difference between re-treatment rates rather than a trend. In addition, a patient's decision to return for reexamination may have

been influenced by a participant's perception of the study group to which he or she was randomized. While the use of patient-driven follow-up and re-treatment after the first 6 months of this study provides a more accurate representation of a true clinical situation, meaningful comparison of our results with existing and future studies utilizing a predefined degree of contracture as recurrence may not be possible. Recurrence is a crucial outcome in many clinical studies on the treatment of DD, and the importance of consistent and standard reporting of disease progression and recurrence has been acknowledged by many authors (Pess et al. 2012; Werker et al. 2012; van Rijssen et al. 2012; Felici et al. 2014).

Finally, the use of patient-reported outcomes in this study would have provided supplementary information on the tolerability of treatment and overall outcomes from the perspective of patients; however, at the time this study was conducted, a validated instrument specific to DD patients was not yet available.

Conclusions

- Relative to those undergoing NA only, patients receiving TA injections with NA experienced significantly less joint contracture between 13 and 24 months and maintained a significantly greater percentage correction throughout follow-up.
- A significantly higher percentage of patients who received NA only returned for re-treatment by 24 months compared with those receiving TA injections
- This study was limited by a decreasing sample size over time and a patient driven follow-up period after 6 months, which may result in biased outcomes.
- Clarifying the long-term outcomes of combining NA with serial TA injections requires a well-controlled randomized study design using an adequate sample size and predefined recurrence to better characterize differences between groups.

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Minimally Invasive Treatment of Dupuytren Contracture: Collagenase Versus PNF

34

Eva-Maria Baur

Contents

34.1 Introduction

Collagenase injection for treating Dupuytren contracture was approved by the European Medicines Agency EMA for the EU in 2011, following an approval by the FDA in 2010 and previous research and trials (Badalamente et al. 2002; Badalamente and Hurst 2007; Hurst et al. 2009; Gilpin et al. 2010). Longer-term studies have been performed (Witthaut et al. 2013; Peimer et al. 2013, 2015). In our series of cases, the application and dose were according to manufacturer's instructions. Only one cord was treated per session and we avoided off-label use.

The origin of percutaneous needle fasciotomy dates back to the middle of the twentieth century when the French rheumatologists De Seze und Debeyre injected cortisone into the cord and subsequently broke the cord by forceful manipulation (de Seze and Debeyre 1957). Results were not satisfying, and the method was improved by Lermusiaux und Defeyre (1980) by punctuating the cord vertically with the needle. The now better results were attributed by Badois et al. (1993) to the punctuation, while the injected cortisone was only helping to suppress inflammation. This method became popular in France, but side effects and high recurrence rates did not make it fully accepted. The current method of using the needle optionally also in a sawing motion and without cortisone injection was described by Lermusiaux et al. (1997) and Foucher et al. (2001).

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34.2 Material and Methods

34.2.1 Recruiting Patients

Outpatients of the University Clinic for Plastic, Reconstructive and Aesthetic Surgery, Innsbruck, needing to get treated for Dupuytren Disease were informed about all possible treatment options. This included partial fasciectomy, the minimally invasive options of collagenase injection and percutaneous needle fasciotomy (PNF) for contracture with palpable cords, and if applicable also radiotherapy for early stage disease. About 40 % of the patients with contracture underwent partial fasciectomy, and 60 % decided for a minimally invasive procedure. The latter were informed about the prospective study "collagenase vs. PNF" and asked to join it. A randomization was not considered feasible and meaningful because patients often already had a clear treatment preference, e.g., for the injection. In the period from 11/2011 to 12/2014, we treated 93 patients minimally invasive and initially included all of them in the study. We excluded cases with recurrence at the same finger or prior treatment of the same hand. Not all patients showed up for follow-up controls; 45 (about 50 %) were lost to FU. 48 patients finally participated (collagenase $n = 25$, PNF $n = 23$), with 58 fingers treated with PNF and 32 fingers with collagenase.

34.2.2 Collagenase Injection

The collagenase injection followed the standard procedure recommended by the manufacturer. On day 1, injection into the cord of 0.58 mg collagenase dissolved in 0.21 ml for PIP joints and 0.25 ml for MCP joints. Local anesthetic was used in case of injection pain, which was in about 25 % of cases. On day 2, at least 24 h after injection, the finger was stretched, usually under local anesthetic or hand block. We performed no off-label application, like injection into several cords or using the full content of 0.9 mg.

34.2.3 Percutaneous Needle Fasciotomy (PNF)

The PNF procedure is slightly different to the standard procedures described elsewhere, e.g., by Eaton (2011a, b). First very little local anesthetic is injected radial and ulnar of the cord(s), just to numb the skin and to avoid regional anesthesia. This helps avoiding nerve damage because the tingling pain when the needle approaches a nerve provides sufficient early warning. Prior to treatment, the patient is informed that this may happen and helps protect his nerves. The finger is stretched to the limit to hold the cord under tension, to pull it up, and to allow the needle to cut. The cord is punctuated and cut horizontally, i.e., vertical to the cord but approaching the cord from lateral/medial in the plane of the palm. The cord is punctuated in a fan-shaped mode using a 20 G needle, which is replaced several times (Baur PNF video 2016). We are using as many portals as necessary to damage the cord sufficiently while stretching the finger. Sometimes the cord ruptures bit by bit, sometimes instantly when the last fibers have been cut. Using the needle more horizontally is additionally beneficial because it allows releasing the dimpled skin from the underlying cord. This limits skin tears to a minimum. The hand is bandaged after the procedure has been completed.

34.2.4 "Postoperative" Care

The same postoperative care is applied for both procedures. A thermoplastic passive splint is adapted to the treated finger and used nightly for at least the next 6 weeks. During the day, the finger and joints are exercised and stretched; the small scar is massaged.

34.2.5 Group Composition

Both groups were of about similar size (collagenase $n = 25$ and PNF $n = 23$), had the same male-to-female ratio of 4:1, and were about equal in age. Staging according to Iselin was a little higher

for the PNF group which also had more affected fingers. Therefore, in the PNF group, the disease was slightly more progressed. In the PNF group, about twice as many fingers were treated than in the collagenase group.

Patients were lost to FU in both groups, but the group compositions remained comparable (Tables 34.1 and 34.2).

34.2.6 Measurements, Recurrence Definition, and Complications

The range of motion/ROM was measured with a goniometer at time 0 (prior to treatment) and 3, 6, and 12 weeks and 6, 12, and 24 months after treatment. The extension deficit was determined for each affected joint as well as the finger-nail-table-distance (stretching the fingers as much as possible and measuring the distance from the finger nail to the table in cm, laying the dorsum of the hand on the table). URAM und Quick-DASH scales were assessed prior to treatment and 6, 12, and 24 months afterward. Clinical success was defined as full stretching of the treated finger or a maximum extension deficit of 10°. The measurement after 3 weeks was the reference for determining recurrence, which was defined as an extension deficit of at least 20° more than at 3 weeks after treatment. This is in agreement with the Rome consensus (Felici et al. 2014). A stable extension deficit, compared to week 3, was not considered recurrence. Complications were recorded 1 and 3 weeks after treatment.

Table 34.1 Patients at 12 months FU

		PNF collagenase	
Patients	48	23	25
Male: female	39:9	19:4	20:5
Age	69	72 (54–80)	67 (49–79)
Right: left hand	27:21	11:12	16:9

Table 34.2 Patients at 24 months FU

		PNF	Collagenase
Patients	27	13	14
Male: female	22:5	11: 2	11: 3
Age	69	72 (56–79)	65 (49–79)

34.3 Results

34.3.1 Treatment Success

Staging of Dupuytren Disease prior to treatment and following Iselin: in the PNF group, there were 21% in stage 2, 61% in stage 3, and 18% in stage 4, whereas in the collagenase group, 40% were in stage 2, 40% in stage 3, and 20% in stage 4. The achieved extension deficits and the development of extension deficits for both treatments were very similar (Figs. 34.1 and 34.2). Quick-DASH results were nearly identical scoring 20 prior to treatment, 3 after 12 months, and 2 after 24 months. The URAM scale improved from 15 to 2 in both groups.

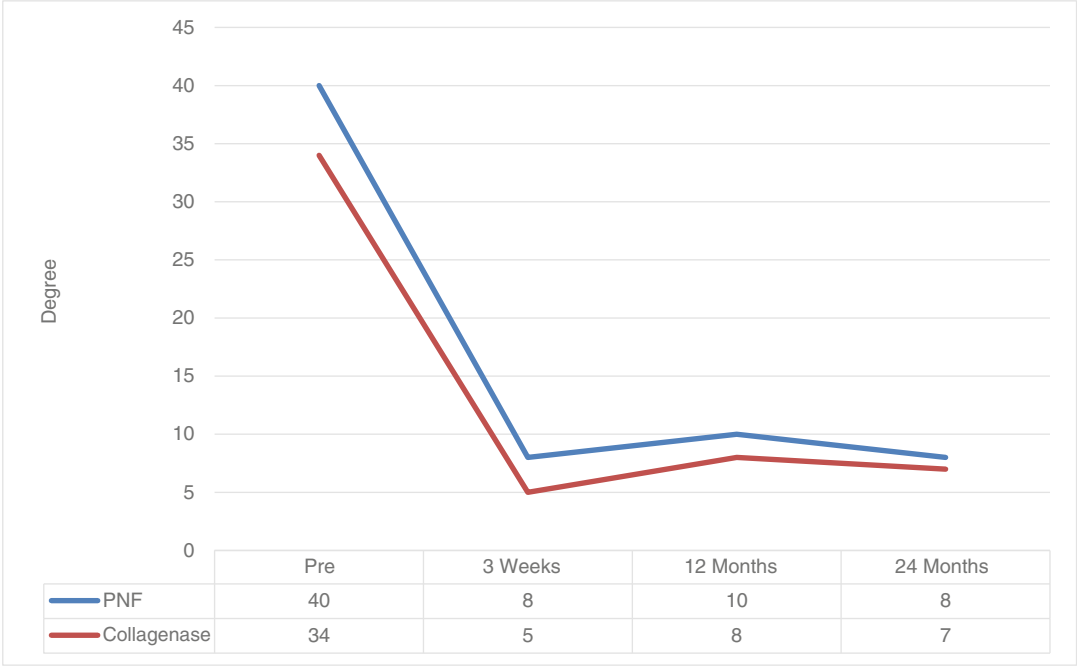
A clinical case for each treatment with photo documentation is shown in Figs. 34.3 and 34.4, respectively.

34.3.2 Complications

There were no major complications, like rupture or damage to tendons, blood vessels, or nerves in either group. In the PNF group, 15% had small skin tears which all healed within a few days. 3 fingers had a slight transient numbing which vanished completely latest within 3 weeks. The collagenase group observed minor complications like swelling and bruising for about 30% of the patients. The assessment of complications and pain was achieved by subjective answers from the patients one week after the treatment. Pain after treatment was much more frequent (5:1) in the collagenase group than in the PNF group.

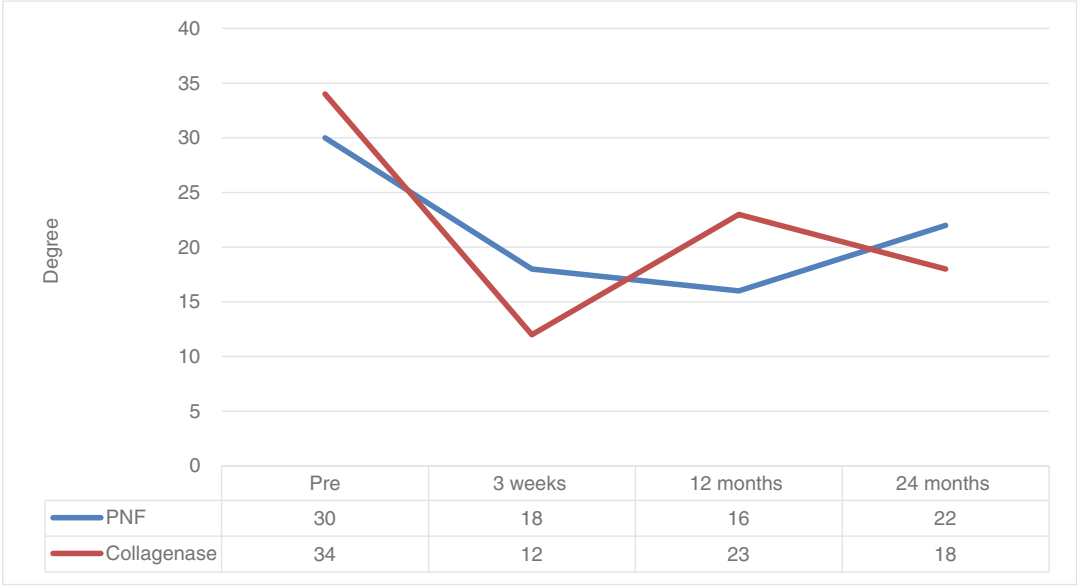
34.3.3 Recurrence, Clinical Success, and Persisting Extension Deficit

Recurrent extension deficits in PIP and MCP joints were very similar in both groups (Tables 34.3 and 34.4). The recurrence results in the PNF group were even slightly better considering the more severe cases in the PNF group than in the collagenase group. Recurrence was measured



	Pre	3 Weeks	12 Months	24 Months
PNF	40	8	10	8
Collagenase	34	5	8	7

Fig. 34.1 Extension deficit before and after 3 weeks, 12 and 24 months for the MCP joint. PNF vs. collagenase



	Pre	3 weeks	12 months	24 months
PNF	30	18	16	22
Collagenase	34	12	23	18

Fig. 34.2 Extension deficit before and after 3 weeks, 12 and 24 months for the PIP joint. PNF vs. collagenase

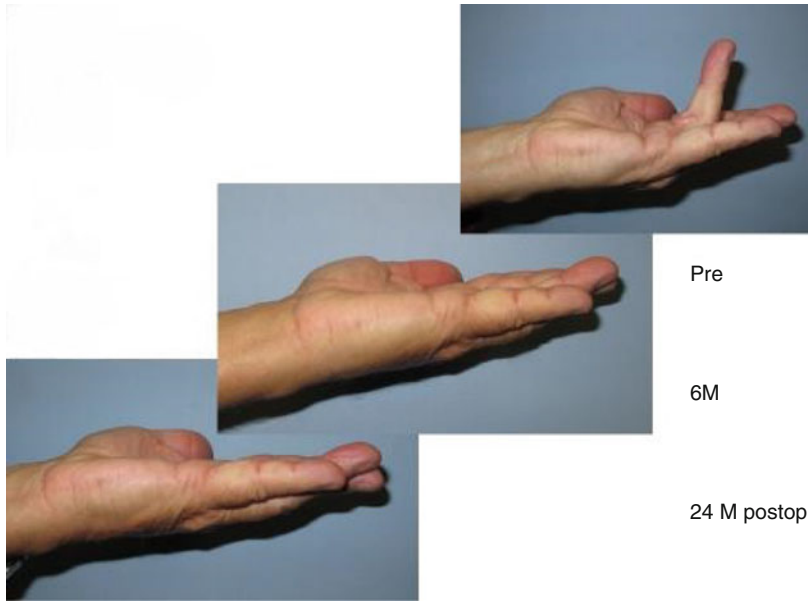


Fig. 34.3 Pre-PNF and post-PNF after 6 and 24 months

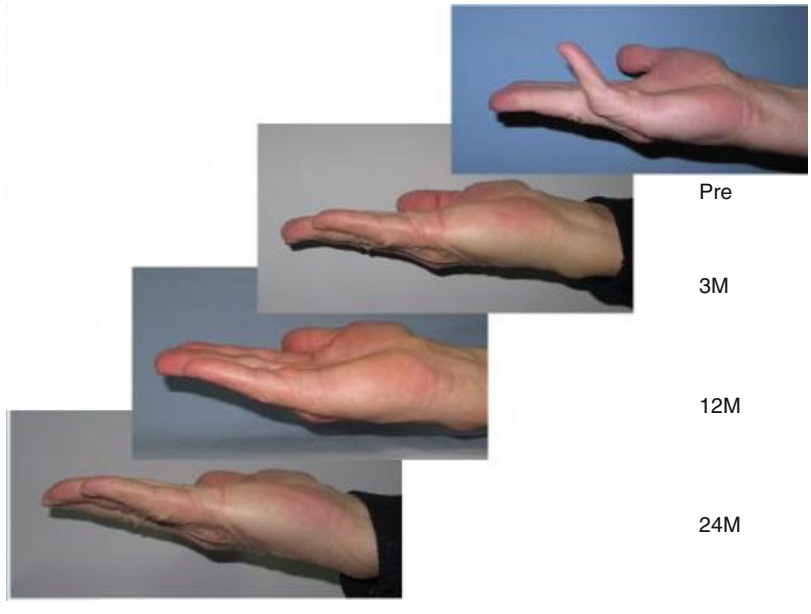


Fig. 34.4 Pre- and post-collagenase injection after 6, 12, and 24 months

Table 34.3 Recurrence for MCP joints

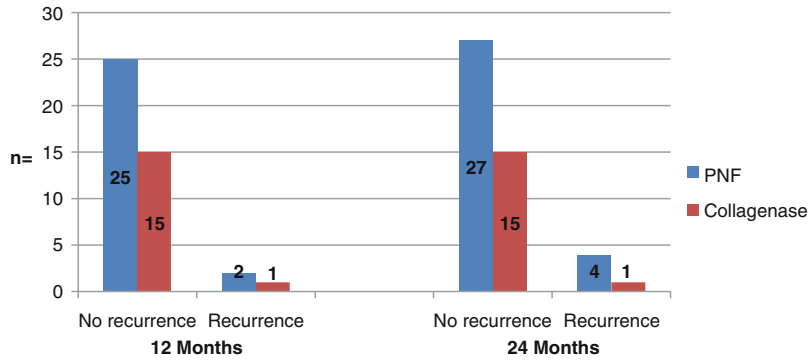
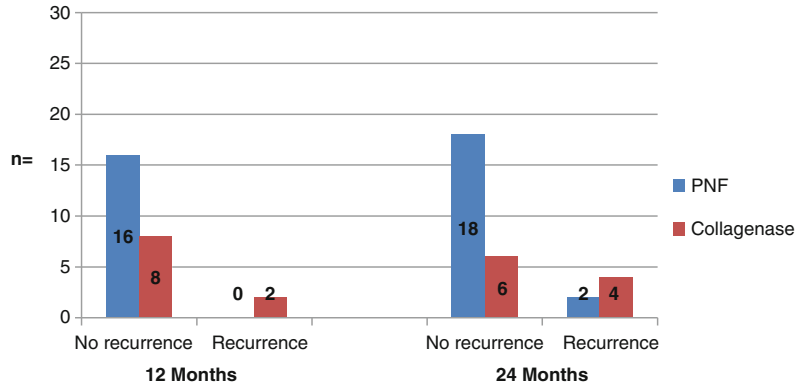


Table 34.4 Recurrence for PIP joints



relative to the result after 3 weeks. No treatment of recurrence was required during the 24-month study, but we are now, after three years, eventually starting to have repeated treatments. Clinical success was considered a straight finger with 0° extension deficit (maximum 10°), and the opposite was a persisting extension deficit after treatment at 3 weeks.

34.4 Discussion

The aim of this study was to compare PNF with collagenase injection. This was achieved by following 2 differently treated but otherwise similar groups over 2 years. For both joints, MCP and PIP, the achieved and maintained extension deficit in both groups was very similar, measured over 24 months. As expected, the MCP joints show better results than the PIP joints, immediately after treatment as well as long term. This is in agreement with the literature (van Rijssen and Werker 2006; Pess et al. 2012; Peimer et al. 2015) where improvements of 80–100 % for MCP and 60–90 % for PIP joints are described. The weaker results for PIP joints can be explained by the anatomy of the side ligaments of the joints.

PNF is a one-session treatment, although this one session may take a little longer than with collagenase injection. PNF can treat several joints and fingers in one session, actually limited only by the patience of the physician and the patient. PNF causes less pain than collagenase injection and is significantly cheaper. This and the application restrictions of collagenase (1 cord per session) resulted in twice as many joints treated in the PNF group although the number of patients was about the same as in the collagenase group. The cost of postop treatment is the same for both treatments.

Our results show very high patient satisfaction with both treatments. This is similar to what is reported in other papers (van Rijssen and Werker 2006; Pess et al. 2012; Peimer et al. 2015). The fast

recovery with little restriction of daily life, work, or hobby results in high satisfaction. The absence from work is much shorter than after fasciectomy, and the limitations in using the hand are much less. Although only the extension deficit is treated and the cords are left in situ resulting in earlier recurrence, many patients, in case of recurrence or disease extension, are choosing the same treatment again. Detailed satisfaction results will be reported elsewhere.

If treated by an experienced hand surgeon, the complication rate is low, according to our own experience and the literature.

With respect to improving the extension deficit, we found very similar results for both treatment options, whereby the PNF group was slightly more progressed and had more fingers affected. Only one other study so far has compared collagenase with PNF by Nydick et al. (2013). It is based on a slightly higher number of patients but less treated fingers and a follow-up period of only 6 months. We consider our follow-up of 24 months as too short allowing only very limited findings on recurrence. As the CORDLESS trial (Peimer et al. 2015) is showing, recurrence increases after two years about linearly.

Overall the number of participants in our study is too low, in part due to the fact that many patients were satisfied after treatment and did not want any further inspection. A bias might also be induced by the increased use of PNF at our hospital. While initially collagenase injection was used for 60 % of the minimally invasive patients and PNF for 40 %, this relation has now reversed and the PNF share is increasing further.

Sometimes it could be helpful, if the result after collagenase injection and the manipulation the day after is not sufficient, to do additional PNF to achieve optimum results.

For the residents, the inauguration of minimal-invasive treatments causes difficulties, because the number of operations becomes significantly less, and especially the "easy" cases are not operated on anymore, but those are the actual cases for teaching. A big opportunity for gaining experience in open procedures and to familiarize with anatomy and pathology is going to be lost but would be beneficial also for minimally invasive treatments. This is similar to the history of the implementation of laparoscopic cholecystectomy.

Conclusion

Collagenase injection introduced a new and successful therapy option for Dupuytren contracture. Additionally it also seems to have triggered a renaissance of the "old-fashioned" percutaneous needle fasciotomy. These two treatment options, if applied by an experienced hand surgeon, are offering a relatively safe treatment with quick recovery and very short restriction of daily life. Results of both treatments are very similar, although the data is still limited. The patient satisfaction is very high, which is also reflected in many patients asking for the same treatment again, if required. Both treatments can easily be repeated provided the cord is palpable.

In summary minimally invasive treatment with collagenase injection or PNF are an excellent means for treating patients with Dupuytren contracture, not for all indications but for most. Both treatments have a high success rate and little risk. They are well accepted by patients and provide high patient satisfaction. In our hospital, they have become a standard treatment for Dupuytren contracture.

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Comparative Effectiveness of Collagenase Injection for Dupuytren Contracture

35

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Contents

35.1 Introduction

Dupuytren Disease remains an incurable fibroproliferative disease involving the palmar and digital fascias of the hand. Abnormal deposition of collagen initially leads to the formation of palpable palmar nodules. With disease progression, cords may develop that cause flexion contractures at the affected finger joints. Ultimately, these contractures can severely impair function and diminish quality of life (Engstrand et al. 2014).

Collagenase clostridium histolyticum (CCH), which selectively disintegrates collagen, is an accepted enzymatic treatment option for Dupuytren contracture (Hurst et al. 2009). The technique involves the injection of a small volume of collagenase solution into the patho-

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logic cord(s), thus weakening the treated areas to allow for subsequent rupture by manipulation. Although several large clinical trials proved the efficacy (performance of an intervention under ideal and controlled circumstances) and safety of collagenase treatment, these studies do not provide evidence on the comparative effectiveness (performance in actual clinical practice) of CCH with the available surgical techniques since they were placebo controlled (Hurst et al. 2009; Gilpin et al. 2010; Witthaut et al. 2013; Warwick et al. 2014).

Limited fasciectomy (LF) is considered the most widely accepted surgical standard of care for Dupuytren Disease. As of this writing, few studies have directly compared LF with CCH. The only two comparative studies we are aware of concluded that the two techniques provide similar results in terms of contracture correction (Naam 2013; Atroshi et al. 2014). However, these studies had small sample sizes ($N=46$ in the largest study), which may have prevented the authors from finding differences due to type II error (failure to detect a difference while it is there due to limited statistical power). Another weakness inherent to such comparative studies using observational data relates to the risk of confounding by indication bias. Because the decision between CCH injection and LF depends partially on patient and clinical characteristics, such as the severity and location of disease, or the number of digits involved, such factors should be accounted for to ensure a valid comparison.

The purpose of this study was to directly compare the clinical results of CCH and LF while using of propensity score matching to minimize confounding by indication bias. Propensity score matching is a statistical approach that allows investigators to account for a large number of observed confounding variables, and is particularly useful in settings where randomization is unfeasible or unethical (Freemantle et al. 2013). In the absence of randomized clinical trials comparing CCH versus LF, this approach allowed for a timely assessment of comparative effectiveness of the two techniques in actual clinical practice (Murphy et al. 2014).

35.2 Methods

After approval of the study by our local institutional review board, we identified all patients with Dupuytren Disease who underwent CCH and LF between 2011 and 2014 at 7 practice sites in the Netherlands using a prospectively maintained database that was designed for research and quality assessment purposes.

Patient factors derived from this database were age, gender, hand dominance, and comorbidities. Disease specific factors included bilateral presence of the disease, primary versus recurrent disease, and family history of Dupuytren Disease. In case data were missing (electronic), health records and office charts were abstracted.

Adult patients with the diagnosis of Dupuytren Disease with the ability to complete the study questionnaires in Dutch were included for the purpose of the study. Exclusion criteria were multiple digit involvement, concomitant hand conditions or interventions (e.g., carpal tunnel release) on the treated side, and the lack of baseline data on the degree of contracture. Patients undergoing treatment for recurrent Dupuytren contracture were included if they met the other eligibility criteria.

35.2.1 Treatments

Treatments were performed as part of standard clinical practice by the hand surgeons of the 7 sites through shared decision-making with the patients. The surgeons involved were European board certified and had extensive experience with different treatment techniques for Dupuytren contracture.

CCH was administered according to manufacturer instructions, without local anesthesia. Injections were limited to 0.25 and 0.20 mL for MP and PIP joint contractures, respectively. Compressive dressings were applied afterward. Treated fingers were manipulated after 24–72 h to attempt rupturing of the weakened cords under local anesthesia. Up to 3 injections were offered at 4-week intervals if patients were dis-

satisfied with the achieved level of contracture correction but were not mandatory. Seven percent of patients received more than 1 injection. An average of 1.08 injections were required, which is similar with the number of injections previously reported in routine practice (Peimer et al. 2013b).

LF – currently the preferred technique for treating Dupuytren Disease in the Netherlands (van Loon et al. 2011) – was performed with tourniquet exsanguination and loupe magnification under axillary block or general anesthesia in an operating theater. Cords were approached and excised after Bruner type or longitudinal incisions with Z-plasties. Care was taken to prevent injury to the digital neurovascular bundles. Compressive dressings were applied for 2 weeks. All patients were offered a similar supervised program of hand therapy with instructed use of removable night splints for 3 months.

35.2.2 Outcome Assessments

Our primary outcome was the degree of residual contracture assessed at follow-up visits occurring between six and twelve weeks after surgery or the last injection. Certified hand therapists assessed the degree of active extension deficit at baseline and follow-up according using a goniometer according to a standardized assessment protocol. Hyperextension was classified as 0° to prevent underestimation of extension deficit.

Secondary outcomes included whether affected joints achieved clinical improvement (defined as a greater than 50% reduction from baseline contracture), adverse events, and self-reported hand function assessed using the Michigan Hand Outcomes Questionnaire (MHQ). The MHQ is a self-reported functioning scale consisting of 37 items evaluating 6 functional subdomains for each hand separately: overall hand function, ability to perform activities in daily life (ADL), work performance, esthetics, pain, and satisfaction with hand function. The MHQ has been rigorously designed and has been thoroughly validated for a variety of hand conditions (Chung et al. 1999) including Dupuytren Disease (London et al. 2014; Thoma et al. 2014). Scores range from 0 (poorest function) to 100 (best function). We excluded all pain outcomes from our analysis, and we only used the outcomes pertaining to the treated side. Adverse events were graded based on their severity into two categories: serious (non-transient or requiring an intervention) and mild (transient or not requiring an intervention).

Given the increasing policy implications of patient satisfaction data (Clapham et al. 2010), we performed a post-hoc analysis of the specific items that constitute the satisfaction subdomain of the MHQ. These items examine satisfaction with overall hand function, finger motion, wrist motion, hand strength, and sensation and are assessed using a 5-point Likert scale, with possible answers ranging from "very satisfied" (1 point) to "very dissatisfied" (5 points). To facilitate and allow for more meaningful interpretation, we classified patients who rated their satisfaction as "very satisfied" (1 point) or "somewhat satisfied" (2 points) as "satisfied" and all others as "dissatisfied".

35.2.3 Statistical Analysis

Continuous variables were reported as means ± SD, and categorical variables were summarized with the use of frequencies. Sample-size calculations demonstrated that a total number of 32 MP contractures (16 each group) and 70 PIP contractures (35 each group) would provide 80% power ($\beta = 0.20$, $\alpha = 0.05$) to detect a 10° difference in residual contracture between the two treatment groups with the use of two-sided tests.

Propensity score matching was used to minimize the risk of confounding by indication bias (Rubin 2007). In this study, the propensity score is defined as the probability of undergoing CCH conditional on 8 pretreatment factors. We used logistic regression modeling to estimate a score for each patient with the treatment type as the independent variable and the following baseline variables as dependent variables: age, gender, family history of Dupuytren Disease, bilateral

involvement, recurrent disease, and the degree of contracture at the three joint levels. The scores were then used to match CCH patients to LF patients on a 1-to-1 basis using a nearest-neighbor approach that allowed for a tolerance width of 0.2SD of the logit of the propensity score. We excluded unmatchable patients from further analysis to minimize bias. To examine whether the matching approach improved balance among the matched treatment groups, we performed significance testing.

For joint contracture and MHQ outcomes, we used a mixed-model repeated-measure approach to compare the outcomes with least-square means and corresponding standard errors plotted graphically. An advantage is that this approach estimates missing values and accounts for the within-patient dependency of the repeated measures to minimize selection bias (Zeger and Liang 1986; Preisser et al. 2002). Joint contracture was evaluated separately for affected MP and PIP joints.

Our primary outcome analysis included all affected joints. However, in some CCH patients with two affected joints in the same finger, one of the contractures was specifically treated with CCH (mostly MP) because the degree of contracture of the other affected joint was improved to such an extent that further injections were deemed unnecessary (Hurst et al. 2009). To assess whether the inclusion of all affected joints in our analysis influenced our results, we performed a subgroup analysis of only the primary targeted joints.

The incidence of serious adverse events was compared between the groups using a Fisher's exact test. Mild adverse events were not compared because many of these were considered to be either specific to CCH or a natural consequence of surgery. Significance thresholds were set at $P < 0.05$.

35.3 Results

We identified a total of 397 patients with Dupuytren Disease who were treated with CCH or LF. To improve comparability among the groups, we excluded 36 % of the patients who underwent LF for contractures involving multiple fingers. After excluding another 9 % of the patients due to the other criteria, a total of 218 eligible patients remained of whom 48 % were treated with CCH and 52 % with LF (Fig. 35.1).

Table 35.1 shows the baseline characteristics of the study sample before and after propensity score matching. Before matching, the CCH group, on average, had relatively milder PIP and DIP joint contractures but worse MP joint contractures. Additionally, fewer CCH patients underwent treatment for recurrent disease, and they differed in terms of which fingers were involved. Using propensity scores, we were able to match 66 CCH patients with mean baseline contractures of 39° degrees for 43 affected MP joints and 41° for 43 affected PIP joints to 66 comparable LF patients with mean baseline contractures of 39° degrees for 39 affected MP joints and 41° for 52 affected PIP joints (Table 35.2).

Ninety-six percent of affected joints in the matched LF group had follow-up data available as compared to 80 % in the matched CCH group. Follow-up duration for both groups was on average 11 weeks (range, 6–12 weeks) and was not significantly different between groups.

35.3.1 Residual Contracture

For affected MP joints, both the degree of residual contracture (CCH, 13° vs. LF, 6°; Fig. 35.2a) at follow-up and the proportion of joints achieving clinical improvement (Fig. 35.3) were not significantly different between the matched treatment groups.

However, for affected PIP joints, the degree of residual contracture was worse in the matched CCH group than in the matched LF group (CCH, 25° vs. LF, 15°; Fig. 35.2b). Accordingly, fewer affected PIP joints achieved clinical improvement in the CCH group than in the LF group (Fig. 35.3).

35.3.2 Self-Reported Outcome

MHQ (sub)scores at baseline were similar between the matched treatment groups. CCH

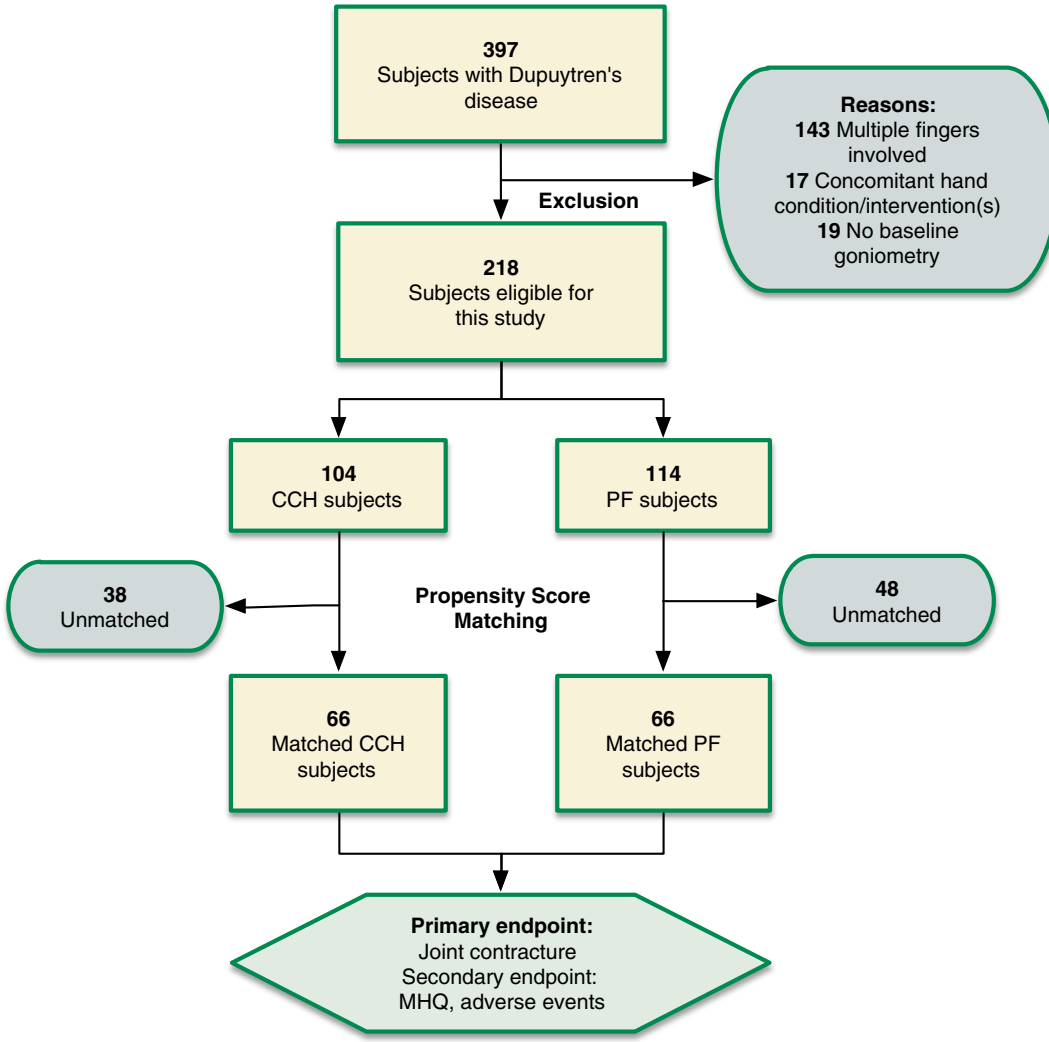


Fig. 35.1 Patient selection flowchart. *CCH* clostridium collagenase histolyticum, *LF* limited fasciectomy, *MHQ* Michigan Hand Outcomes Questionnaire

patients reported significantly larger improvements from baseline than did LF patients in the subscores of satisfaction, ADL, and work performance (Fig. 35.4).

The proportion of patients who were satisfied with items constituting the satisfaction subdomain of the MHQ was similar at baseline between the matched treatment groups (Fig. 35.5). The proportion of patients who were satisfied with their finger mobility and hand function showed a similar increase at follow-up among the two treatment groups. However, as compared with LF patients, relatively more CCH patients were satisfied with their hand strength and sensation.

35.3.3 Adverse Events

Table 35.2 lists the adverse events noted in the matched groups, graded by severity. All serious adverse events occurred after LF; three events of tenosynovitis requiring an intervention and one nerve injury were noted as compared with zero events after CCH ($P = 0.042$). Arterial

Table 35.1 Baseline characteristics before and after propensity score matching, by treatment group

	All patients			Matched patients		
	CCH ($N=104$)	LF ($N=114$)	*P* value	CCH ($N=66$)	LF ($N=66$)	*P* value
Demographics						
Age – years	61 ± 10	63 ± 9	0.410	61 ± 10	63 ± 8	0.334
Male gender – %	80	81	0.868	82	76	0.394
Diabetes – %	3	9	0.087	6	5	0.698
Current tobacco use – %	9	16	0.090	8	15	0.170
Disease characteristics						
Recurrent disease – %	26	38	0.063	33	30	0.709
Bilateral disease – %	85	83	0.797	89	89	1.000
Treated side is dominant – %	58	53	0.453	53	61	0.380
Positive family history Dd – %	54	60	0.388	59	49	0.222
Treated finger			0.003			0.789
Little – %	48	72		55	61	
Ring – %	37	24		33	32	
Other – %	15	4		12	8	
Outcomes at baseline						
Contracture[a] – degrees						
MP joint	29 ± 24	19 ± 27	0.002	26 ± 25	23 ± 25	0.632
PIP joint	22 ± 25	44 ± 27	<0.001	27 ± 26	33 ± 25	0.221
DIP joint	1 ± 4	8 ± 14	<0.001	1 ± 14	2 ± 14	0.547
Total MHQ score (0–100)	75 ± 14	74 ± 15	0.844	77 ± 13	75 ± 14	0.545

Plus-minus values are means ± SD

CCH collagenase clostridium histolyticum, *LF* limited fasciectomy, *Dd* Dupuytren Disease, *MP* metacarpophalangeal, *PIP* proximal interphalangeal, *DIP* distal interphalangeal, *SD* standard deviation, *MHQ* Michigan Hand Outcomes Questionnaire

[a]Values are reported for all joints

injuries, cold intolerance complaints, and tendon ruptures were not seen in either of the matched groups.

Three of the most frequently noted mild adverse events after CCH were peripheral edema (74%), contusion (64%), and extremity pain (26%).

35.3.4 Subgroup Analysis of the Joints Affected by Recurrent Disease

Evaluating only the joints affected by recurrent disease, we found no significant differences in the baseline degree of contracture among the matched treatment groups, although affected MP joints were on average 8° worse in the CCH subgroup than in the LF subgroup.

Comparison of these two groups showed that while the degree of residual contracture at follow-up was not significantly different for affected MP joints (CCH, 19° vs. LF, 10°; Fig. 35.6a), affected PIP joints in the CCH subgroup were significantly worse as compared with those in the LF subgroup (CCH, 33° vs. LF, 22°; Fig. 35.6b).

35.3.5 Subgroup Analysis of Primary Targeted Joints

Evaluation of only the affected joints specifically targeted with CCH also showed a similar degree

Table 35.2 Adverse events, by matched treatment groups

Adverse event	CCH ($N=66$)	LF ($N=66$)
Serious		
Tenosynovitis	0 (0)	3 (5)
Nerve injury	0 (0)	1 (2)
Arterial injury	0 (0)	0 (0)
Tendon rupture	0 (0)	0 (0)
Cold intolerance	0 (0)	0 (0)
CRPS	0 (0)	0 (0)
Mild		
Peripheral edema	49 (74)	n.a.
Contusion	42 (64)	n.a.
Extensive	3 (5)	n.a.
Mild	39 (59)	n.a.
Pain in extremity	17 (26)	n.a.
Blood blister	9 (14)	n.a.
Skin fissure	5 (8)	0 (0)
Paresthesia	3 (5)	3 (5)
Axillary tenderness	6 (9)	n.a.
Erythema	3 (5)	n.a.
Wound dehiscence	0 (0)	2 (3)
Pruritus	3 (5)	n.a.
Lymphadenopathy	2 (3)	n.a.
Neuropraxia	0 (0)	1 (2)
Flare reaction	1 (2)	0 (0)

CCH collagenase clostridium histolyticum, *LF* limited fasciectomy, *CRPS* complex regional pain syndrome, *n.a.* not assessed

[a]Values are numbers (percentages)

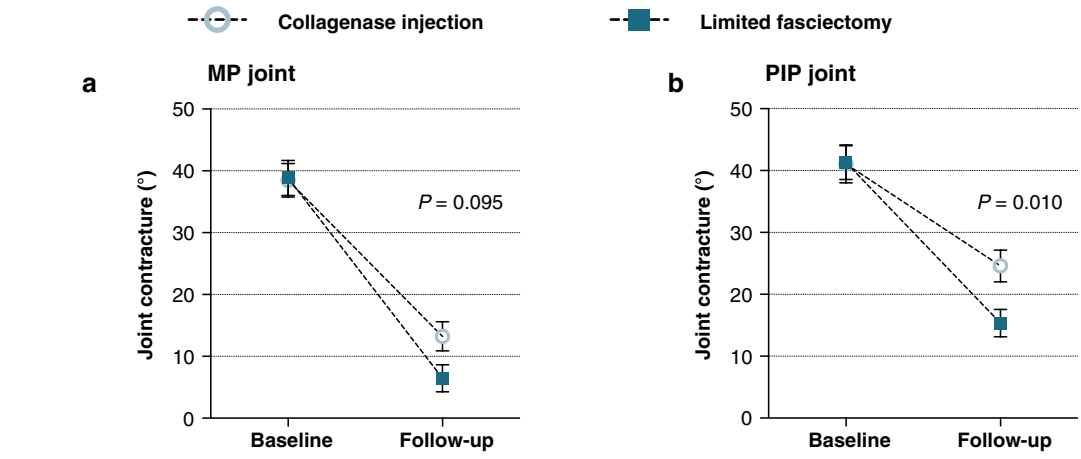
of residual contracture as compared to all affected MP joints in the LF group. However, the PIP joint contractures that were specifically targeted with CCH showed significantly worse residual contracture as compared with the LF group.

35.4 Discussion

Because clinical practice may not mirror the strictly controlled settings of clinical trials, interest in comparative effectiveness research has exploded in recent years (Volpp 2009; Zhou et al. 2016). The aim of this study was to compare the effectiveness of CCH and LF, while accounting for the differences in baseline factors contributing to treatment selection bias using propensity score matching (Rothwell 2005). The primary finding was that the degree of residual contracture in the two treatment groups was not significantly different for contractures at the MP joint level, while affected PIP joints showed a significantly worse residual contracture in the CCH group as compared with the LF group. Nevertheless, patients in the CCH group reported larger functional improvements than did LF patients at early follow-up and experienced fewer serious adverse events.

Previous comparative studies on CCH have reported 10° of residual contracture for affected MP joints of and 23–26° for affected PIP joints (Nydick et al. 2013; Atroshi et al. 2014) at early follow-up, which is consistent with the 13° and 24° found in the present study. The 6° and 15° for affected MP and PIP joints found in our LF group is consistent with the 5° and 14° degrees reported at 6 weeks follow-up by van Rijssen and colleagues (van Rijssen et al. 2006). However, our finding that LF was superior to CCH for affected PIP joints contrasts the few available studies comparing the two techniques (Naam 2013; Atroshi et al. 2014). Although one retrospective study found that LF achieved an average of 9° more contracture reduction after examining a total number of 24 affected PIP joints, this difference was not significant (Nydick et al. 2013). The only other study we are aware of reported similar results after evaluating a total of 18 affected PIP joints (Atroshi et al. 2014). In comparison, the present study included more patients with PIP joint involvement and was therefore more powered to detect significant differences. An explanation for these findings is that the two procedures are fundamentally different from each other: CCH is a closed technique relying in part on enzymatic fasciotomy/fasciolysis, whereas an open fasciectomy allows for extensive excision of the diseased tissue and ancillary surgical efforts, such as the division of the collateral and check-rein ligaments and occasionally the release of the volar plate, to maximize contracture correction.

As compared with those who underwent LF, CCH patients reported larger functional improvements in the MHQ subdomains assessing ADL, work performance, and satisfaction with hand



No. Joints		
Collagenase injection	43	32
Limited fasciectomy	39	37

No. Joints		
Collagenase injection	43	38
Limited fasciectomy	52	50

Fig. 35.2 Degree of contracture for affected metacarpophalangeal (**a**) and proximal interphalangeal (**b**) joints. Matched collagenase injection and limited fasciectomy groups at baseline and follow-up. Least-square means and standard errors from a repeated-measure model are plotted

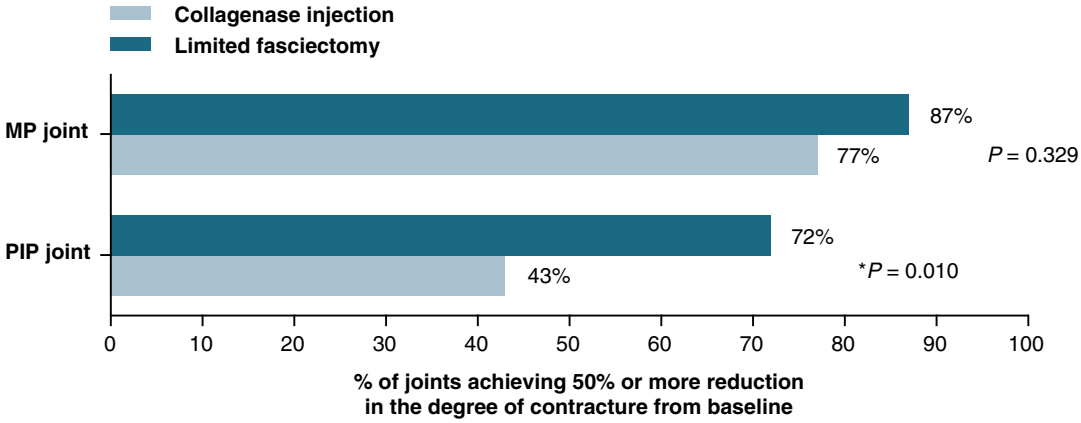
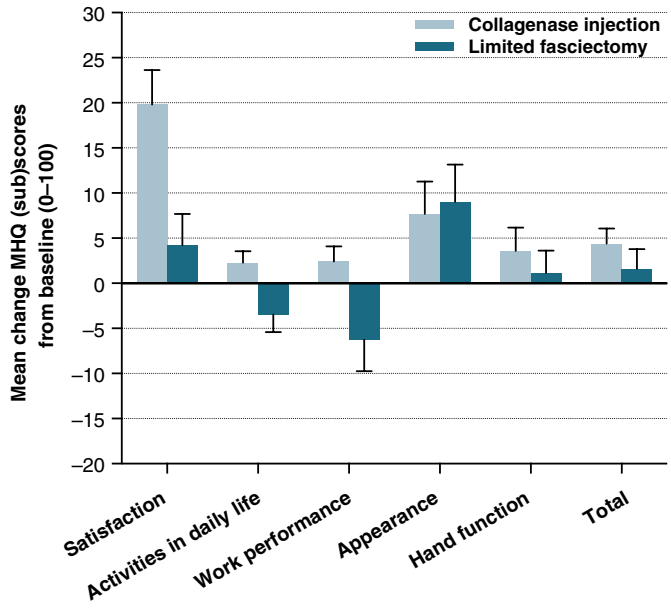


Fig. 35.3 Percentage of affected joints meeting clinical improvement

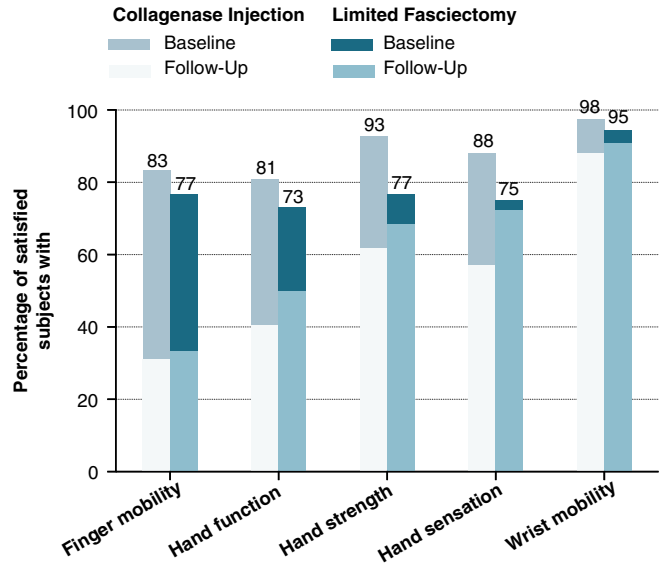
function at follow-up. We believe that this finding primarily shows that hand function recovers more rapidly after CCH than after LF, which may be an important reason for patients to opt for CCH. The similar improvement in appearance subscores suggests that both treatments address concerns patients may feel about the appearance of their hand as a consequence of their contracture Zhou et al. (2015).

This study has several drawbacks worth considering. First, we included both patients with primary and recurrent disease to increase the generalizability of our study. Although subgroup analyses of only the patients with recurrent disease showed that the comparative effectiveness of the two techniques was similar to that in the overall groups, such analyses remain exploratory, thus indicating the need for larger studies to confirm these findings in recurrent cases. Second, the relatively higher incidence of serious adverse events found in the LF group warrants careful interpretation due to the small number of events, but is consistent with a previous systematic review showing that CCH has a more favorable risk profile than LF (Peimer et al.



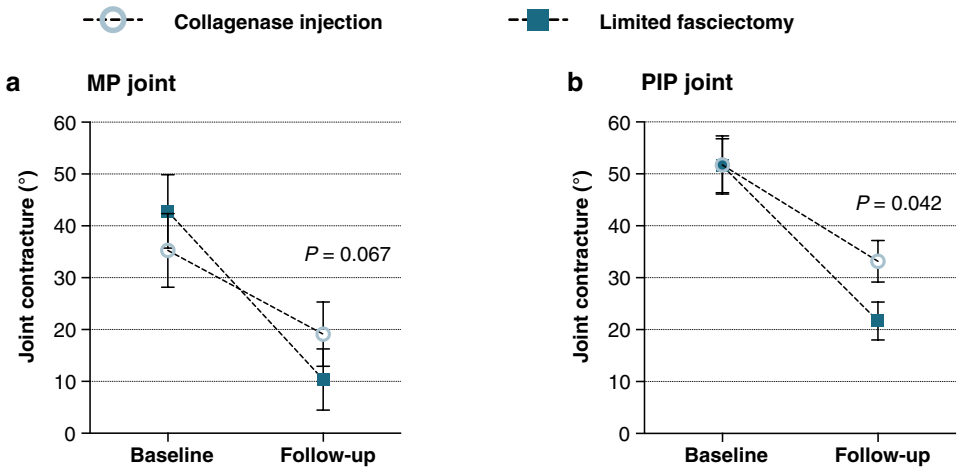
Change in MHQ score						
Collagenase injection	19.8	2.3	2.4	7.7	3.6	4.4
Limited fasciectomy	4.2	–3.5	–6.3	9.0	1.2	1.6
P Value	*0.003	*0.033	*0.029	0.821	0.506	0.363

Fig. 35.4 Change in MHQ scores. Change in MHQ scores in the matched collagenase injection and limited fasciectomy groups at follow-up as compared with baseline. Asterisks (*) denote significant differences between the matched treatment groups



% Increase from baseline					
Collagenase injection	52	41	31	31	9
Limited fasciectomy	44	23	8	3	4

Fig. 35.5 Proportions of satisfied patients. The proportion of patients who were satisfied with five specific items constituting the satisfaction subdomain of the Michigan Hand Questionnaire in the matched collagenase injection and limited fasciectomy groups at baseline and follow-up



No. Joints		
Collagenase injection	10	8
Limited fasciectomy	10	9

No. Joints		
Collagenase injection	18	15
Limited fasciectomy	20	19

Fig. 35.6 Degree of contracture of joints affected by recurrent disease. Degree of contracture for metacarpophalangeal (**a**) and proximal interphalangeal (**b**) joints affected by recurrent disease in the matched collagenase injection and limited fasciectomy groups at baseline and follow-up. Least-square means and standard errors from a repeated-measure model are plotted

2015). Third, our study only evaluated early clinical outcomes. Although a better initial contracture correction may predict a lower risk of recurrence (Dias and Braybrooke 2006; Dias et al. 2013; Peimer et al. 2013a, b), the relative long-term effectiveness of CCH remains unknown as meaningful comparisons between studies are impeded by the wide variety of outcome definitions used and the heterogeneity of the study samples (Becker and Davis 2010; Werker et al. 2012; Kan et al. 2013; Henry 2014). Fourth, our matching approach resulted in the exclusion of a sizeable proportion of patients with severe PIP joint contractures in the LF group for which LF was the preferential treatment. As such, our study findings do not apply to cases with advanced PIP contractures. Fifth, it should be noted that the results of the CCH group reflect the injection technique as currently recommended by the manufacturer, that is, injecting only in one part of the cord. Recent recommendations including injection into multiple areas and concurrent injections might translate into more favorable results, which should be explored by future comparative studies (Murphy et al. 2014; Gaston et al. 2015). Finally, although collagenase treatment offers good results for cords affecting the thumb, these ought to be compared with the results achieved by its surgical alternatives to provide more nuanced information to improve clinical decision-making (Dreise et al. 2016).

Conclusion

Taken together, this study suggest that CCH provides a less invasive alternative to LF for patients with MP contractures, as well as those with PIP contractures who are willing to trade better contracture correction for a lower risk of serious adverse events and faster recovery of hand function. Besides a comparison of treatments, this study highlights the use of propensity score analyses for making inferences on the effectiveness of treatments for Dupuytren Disease in the real world (Freemantle et al. 2013).

Conflicts of Interest Declaration We declare that several coauthors (S.E.R.H., R.W.S., R.F.) have been consultants to Pfizer and Sobi, two manufacturers of injectable collagenase in Europe, after agreeing not to personally receive any form of financial compensation for their advisory services. Support was received from Pfizer in the

form that the injections used in the present study were provided free of charge. To ensure objectivity, the present study was conducted without any involvement from both pharmaceutical companies.

This chapter is an extended and updated version of the paper Zhou C et al. (2015) Collagenase Clostridium Histolyticum versus Limited Fasciectomy for Dupuytren's Contracture: Outcomes from a Multicenter Propensity Score Matched Study. Plast reconstr surg 136:87–97 and is reproduced with permission of the American Plastic Surgery Society and Wolter Kluwer.

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Short-Term Cost-Utility Analysis of Collagenase Versus Fasciectomy for Dupuytren Contracture

36

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36.1 Introduction

The use of collagenase clostridium histolyticum (CCH) provides advantages of noninvasive treatments (rapid recovery, low incidence of severe complications, and minimal alteration of the skin), while fasciectomy (FSC) provides removal of the diseased tissue and a lower recurrence rate. CCH is increasingly being used in hand care units (Schulze and Tursi 2014). Creating protocols adapted to small surgery units, or even outpatient units, has allowed optimizing both the clinical and economic results of its use (Sanjuan-Cervero et al. 2013). Various studies have assessed the costs associated with treatment of Dupuytren contracture (DC) with regard to a single technique (De Salas-Cansado 2013; Sanjuan-Cervero 2013; Atroshi 2014; Eckerdal 2014). Very few have evaluated the efficiency of CCH compared to fasciectomy (Chen 2011; Baltzer and Binhammer 2013). So far, no studies regarding cost-effectiveness have been performed in Europe that could help in the decision-making process in treating DC.

The main aim of this cohort study at our hospital in Spain was to determine which option is more cost-effective for treatment of Dupuytren contracture, partial fasciectomy, or single administration of CCH. The follow-up period is 6 months. For this purpose, we use a pharmacoeconomic model.

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DOI 10.1007/978-3-319-32199-8_36

36.2 Material and Methods

This is a cohort study with a retrospective group, FSC patients, and a case group, CCH patients. Data on CCH injections were collected prospectively. Ninety-one patients were included in the study: 43 FSC patients and 48 CCH patients. Both groups were comparable statistically in all terms except in the time of procedure (Table 36.1). The FSC group was composed of patients treated within a two-year period, selected by reviewing clinical data. The CCH group started once we had adopted a protocol for treatment with CCH. The effectiveness was defined as a reduction in the degree of contracture of at least 66 %, measured as a percentage of the initial contracture with regard to the end contracture. We only used one injection of CCH per finger and in the FSC group included only patients treated at one finger per surgery to homogenize groups. The follow-up time was six months from the intervention with periodical reviews in the clinics at 2 and 4 weeks and after that at 2 and 6 months.

The treatment results were assigned to 8 and 6 treatment scenarios for FSC and CCH, respectively, taking into account possible complications (Chen et al. 2011) (Fig. 36.1). The study was based on the healthcare system in Spain. All relevant direct medical costs for both alternatives were collected in 2014 and in €. Unit costs were obtained from the Pharmacy Service and Accounting Department of the hospital. An analysis of sensitivity was performed by modifying the main variables to check the robustness of the results.

Cost collected for both groups were: initial traumatology visit at the clinic, wound healing, physiotherapy sessions, subsequent visits, recurrence and main complications. For the FSC group specific costs included were: general or plexus block anesthesia, preoperative tests and operating room costs. For the CCH group the costs were based on the acquisition, preparation and administration of the drug and local anesthesia costs for the extension of the finger. (De Salas-Cansado et al. 2013; Sanjuan-Cervero et al. 2013).

We calculated QALYs for each possible outcome by multiplying the mean utility assigned by the participants by 20 remaining life years (Chen et al. 2011). We calculated incremental cost-effectiveness ratios (ICER) by dividing the incremental costs of the intervention by the incremental benefits, such as €/QALYs (Husereau et al. 2013).

Table 36.1 Demographic and clinical variables according to the type of treatment

Variable	FSC ($N=48$)	CCH ($N=43$)
Age (mean + SD)	65.9 (9.2)	65.1 (9.7)
Sex (male %)	83.3	88.4
Number of affected digits	64	50
Affected digits (average per patient)	1.33 (0.48)	1.16 (0.4)
Affected joints:		
MCP	5 (10.4 %)	7 (16.3 %)
PIP	14 (29.2 %)	12 (27.9 %)
MCP + PIP	29 (60.4 %)	24 (55.8 %)
Contracture		
MCP	34 (70.8 %)	31 (72.1 %)
20–30	6 (17.6 %)	8 (25.8 %)
30–60	13 (38.2 %)	10 (41.9 %)
>60	15 (44.1 %)	13 (41.9 %)
PIP	43 (89.6 %)	36 (83.7 %)
20–30	9 (20.9 %)	6 (16.6 %)
30–60	20 (46.5 %)	16 (44.4 %)
>60	14 (32.5 %)	14 (38.8 %)

No statistically significant differences between groups ($p<0.05$)

36.3 Results

FSC was effective in 87.5 % and CCH was effective in 67.4 % of patients. Complications and recurrences (18.8 % and 14.6 % FSC; 18.6 % and 11.6 % CCH, respectively) were similar in both groups. The main cost of the CCH group was drug cost (62.5 %). 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.

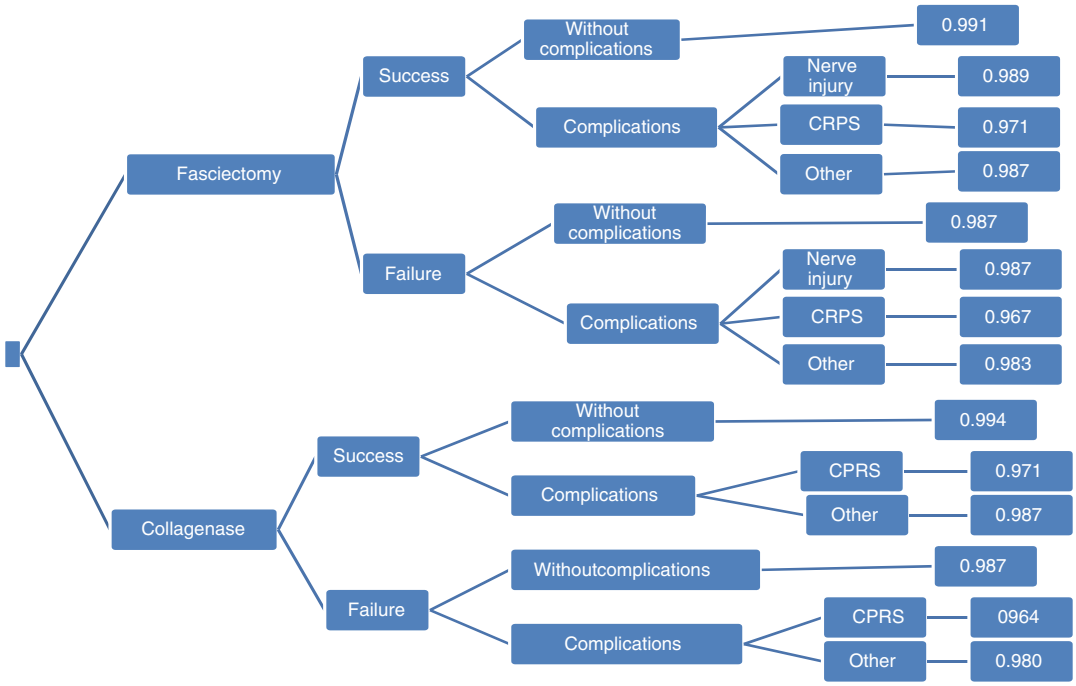

Fig. 36.1 Treatment scenarios (Numbers on the right side are the utility values as determined by Chen et al. (2011))

Mean cost per patient obtained was 1420.19 € for the FSC group (CI 95%: 1127.64–1709.65) and 1161.72 € for the CCH group (CI 95%: 1034.35–1317.71) (Fig. 36.2). The mean utilities obtained were 0.9892 (SD: 0.0050) and 0.990 (SD: 0.0064) QALYs for FSC and CCH, respectively. The sensitivity analysis of key variables shows the robustness of our results.

At the end of the follow-up and after 20 years, we find negligible differences in mean utilities for both groups, probably due to the small sample size. After 20 years, these savings were 6190.39 € per QALY gained (CI 95%: −31607.47 to 19226.70). In conclusion, CCH is the dominant option at the short and long term in the sample studied at our hospital.

In the univariate sensitivity analysis performed, the variable with a greater influence on the final result, regardless of the point in time when the analysis took place, was observed to be the cost of collagenase acquisition. Other variables that might impact the decision, but to a lesser extent, were the cost of physiotherapy sessions and the cost of the operating room.

36.4 Discussion

Our study is based on a pharmacoeconomic model. A pharmacoeconomic model is only a representation of the reality; its validity depends on how reasonable the assumptions are and only whether they help simplifying complex medical events (Rubio-Terres 2000).

In a previous study, we already observed how CCH treatment was more economic than treatment with fasciectomy (Sanjuan-Cervero et al. 2013). With regard to cost-utility models, we have used Chen's model (Chen et al. 2011) as a basis to perform our study, with similar conclusions: the use of only a single CCH vial is more cost-effective than the fasciectomy treatment, especially when the price per vial is less than $945 (approx. €850). Baltzer and Binhammer (2013) used a cost-utility analysis approach to compare for Canada's cost-effectiveness of partial fasciectomy, needle fasciotomy (PNF), and CCH, identifying PNF as the preferred strategy for managing contractures affecting a single finger, indicating however that the use of CCH

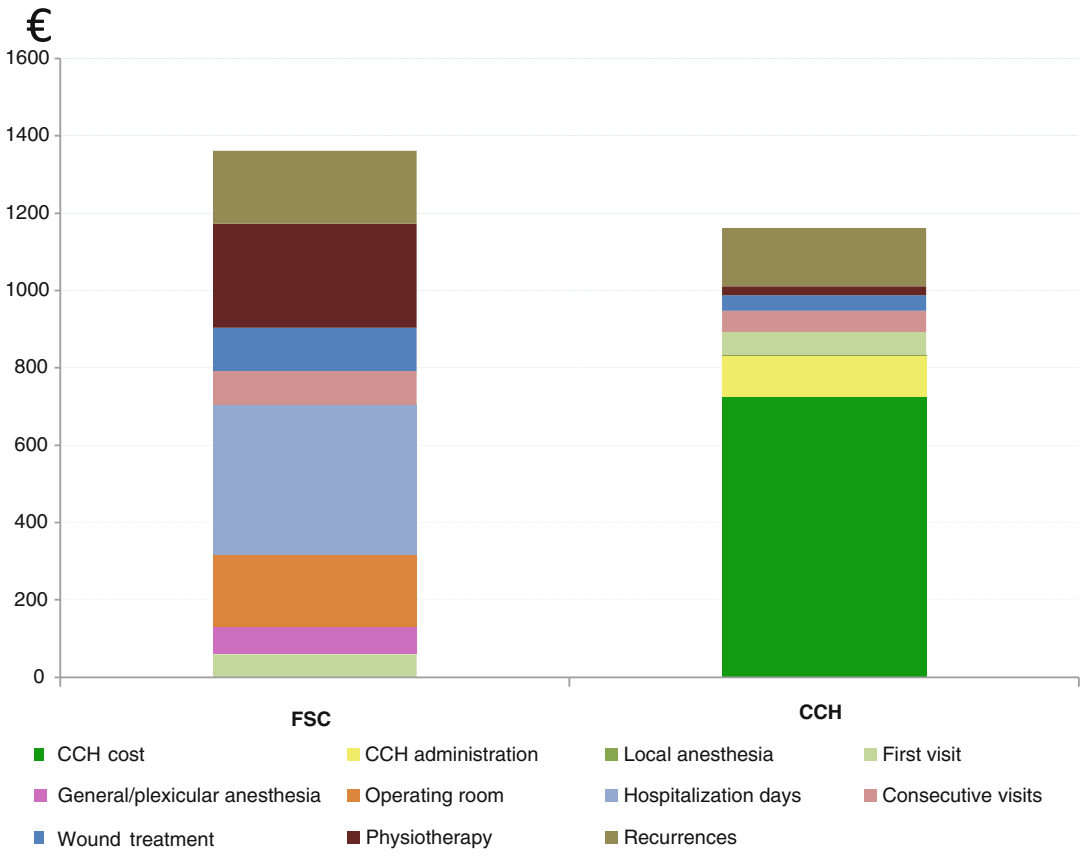

Fig. 36.2 Mean cost/patient (costs in € as of 2014)

becomes cost-effective below a vial price of $875 (€775). Malone and Armstrong (2012) concluded that treatment with CCH is most economic and having a slight association with greater QALYs than other treatments assessed. Treatment with a single CCH injection has an estimated cost of 33% less than fasciectomy, with a similar efficacy at six weeks' progression (Atroshi 2014).

Our results cannot be extrapolated to other countries, since the price of CCH, the most influential factor for this treatment, varies considerably from one country to another.

The main limitation of our study is the short length of follow-up time. Also, indirect costs, or costs associated with social and employment perspectives of patients, have not been included. These would probably favor CCH due to the rapid recovery time and the little need of external resources. Finally, the comparison of surgery and CCH always has significant limitations, even when considering just economic aspects. It could be argued that CCH treatment is for a single cord and not for a complete treatment of a finger like FSC. We have tried to minimize this bias evaluating results by Tubiana classification including all the fingers affected and not only the cord treated.

Conclusions

- After following patients for 6 months, CCH was more efficient than FSC in DC treatment for a single finger at our hospital.
- The total cost of CCH treatment with more than one vial pushes ICER above the threshold (30.000€/QALY).

Acknowledgments and Conflict of Interest Declaration The authors declare that they have no conflicts of interest to report.

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An Easy Way for Clinical Validation of the Pharmacoeconomic Model in Dupuytren Disease

37

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37.1 Introduction

The traditional way in which clinical validation takes place in pharmacoeconomics has always been to gather expert clinical opinions on the disease so that models take into account all possible events, both favorable and unfavorable, including secondary effects. These methods vary in the extent to which panels of experts adopt strict, formal, and explicit standards for interacting and communicating in order to reach a consensus.

Among the different consensus methods, the RAND appropriateness method and the Delphi method (Camps-Herrero et al. 2014) are the most popular ones. The Delphi method is occasionally modified to more than one round, in order to analyze the preferences of the experts and achieve a proper clinical validation. Delphi is a high-cost methodology because of the time expenditure of the experts required for its realization.

The aim of this paper is finding a more versatile way to evaluate (or validate) treatment options. A statistical exercise is presented to provide a valid and survey-based alternative to the Delphi method or a means to evaluate expert opinion prior to a Delphi consensus. As an example, a simple tree decision model is used to compare two treatments for Dupuytren contracture (DC) with the aim of clinically validating two different pharmacoeconomic models. No clinical validation has been formally conducted. The

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results of this survey allow unifying ideas prior to the realization of a Delphi method.

37.2 Material and Methods

We examine two decision trees used to compare surgical treatment (fasciectomy) with collagenase injection (CCH) for treating DC. Model 1 is simpler, it reflects the success or failure of therapy, and complications are generally assumed to be the same. Model 2 provides more details on the types of complications.

We conducted a cross-sectional study to learn about the preferences of orthopedists with regard to treatment for DC. A guided interview on two possible decision trees for treating DC was used. For clinical validation of both models, we used a survey that included six attributes.

- Structural simplicity: Which is less complex?
- Comprehensibility: Which is less confusing?
- Adaptability: Which provides better health outcomes?
- Reliability: Which best measures possible outcomes?
- Extrapolation to other countries: Which do you think can best be extrapolated to other countries or other health systems?
- Applicability: Which is better suited to helping you care for patients?

We compared and analyzed the results and the validity of the questionnaire employed. To better communicate both models, they were explained by an orthopedic surgeon before the questionnaire was administered. Mean scores were analyzed using the *t*-test for paired samples. To check the consistency of scores, Cronbach's alpha and the intraclass correlation coefficient to measure the degree of agreement were used (Figs. 37.1 and 37.2).

37.3 Results

The questionnaire to assess the models was answered by 27 orthopedic surgeons. Only five residents responded to the survey, and the rest of the surgeons had an average length of practice as specialists of 10.1 (minimum: 0; maximum: 30) years (Fig. 37.3).

The total score obtained was 35.49 (CI 95 %: 32.33–38.64) for model 1 and 38.72 (CI 95 %: 35.78–41.65) for model 2 (the difference was not statistically significant). Upon analyzing the pattern of the responses for the items, no floor or ceiling effects were observed. The standard error of measurement (systematic and random error of a participant's score that is not attributable to true changes in the construct to be measured (Mokkink et al. 2010)) was calculated at 0.796, which is 8.0 % with respect to the global for the scale. The

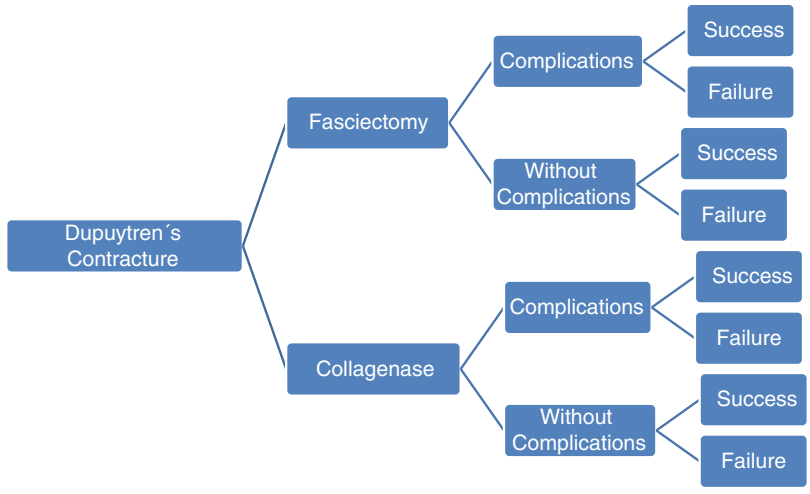

Fig. 37.1 Model 1 (simple model)

minimal detectable change (magnitude of change required to be 95 % confident that the observed change between the 2 measures reflects real change and not just measurement error (Haley and Fragala-Pinkham 2006)) was 2.21 (Fig. 37.4).

Corrected item-total correlation for the two pharmacoeconomic models shows a linear relationship between structural simplicity and comprehensibility. The total Cronbach's alpha was 0.803 for model 1 and 0.805 for model 2.

Globally, there were no significant differences between the scores given to both models. No different results were found relative to the level of care at the hospitals to which the surgeons belonged or their experience as practitioners. The internal consistency of the scores was moderately high; Cronbach's alpha based on standardized items was 0.741. The intraclass correlation coefficient (average measures) to assess the agreement between the two models was 0.614, and for consistency, it was 0.727, with both being statistically significant ($P<0.05$).

37.4 Discussion

We have used two statistical analyses: a descriptive analysis applied to the results obtained from the questionnaire and a factorial analysis for the assessment of the tool's reliability index through calculation of Cronbach's alpha (Cronbach 1951). Two decision-making trees were used, since they explain acute surgical and medical events, such as DC, in a better way than other methods (such as Markov models). Furthermore, these provide the advantage of maximum flexibility in the design, as well as a greater interpretability by clinicians (Carrera-Hueso and Ramon 2011). Our results do not demonstrate the superiority of one pharmacoeconomic model over the other in terms of the total scores obtained from the survey. However, there are significant differences in the scores awarded to both on different scales. We found no differences in scores in terms of the characteristics of the physicians surveyed or with regard to their experience or the level of healthcare of the hospital. Model 1, the simpler one, had better scores for structural simplicity and comprehensibility. This model has been used in other pharmacoeconomic studies published regarding DC (Chen et al. 2011; Baltzer and Binhammer 2013). Model 2 had better scores for adaptability and reliability, apparently because it better reflects actual clinical situations.

One of the methods most used to collect and analyze these preferences is using expert opinions, as is done in the Delphi method (Camps-Herrero et al. 2014; Hay 2004). We have applied

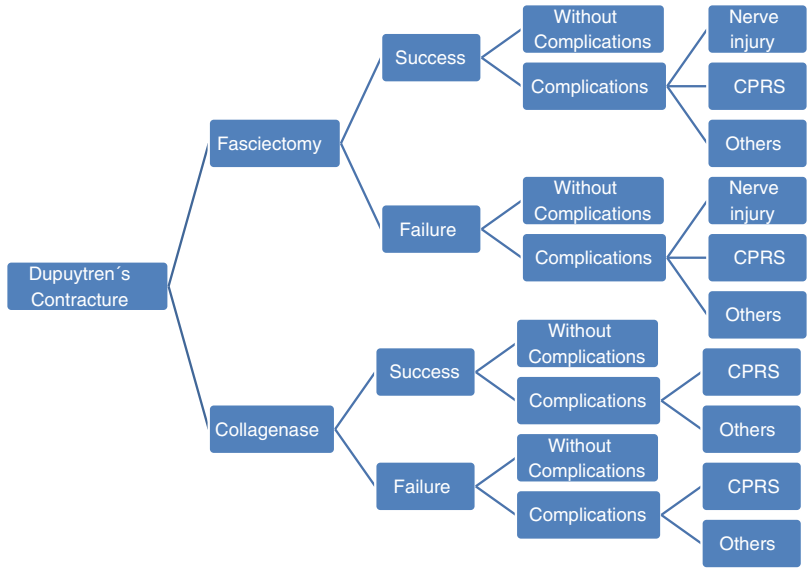

Fig. 37.2 Model 2 (including details on complications)

the study from a pharmacoeconomic point of view, but the applications are much broader. Our work shows the possibility of performing a survey on experts in a given field as an alternative, or preliminary step, to performing the Delphi method or any other method. Carrying this out during the meetings of experts could also allow for a preliminary discussion forum, thus helping to unify ideas and answer any questions, as occurred at the international conference on Dupuytren Disease, in a safe, easy, and low-cost way.

Among the limitations of our study were the small sample size used and the absence of a reference test on Dupuytren Disease that would allow us to objectively measure the validity of the questionnaire used in our study. While the sample is not completely uniform, it is difficult to find representative samples. Surgeon respondents were all knowledgeable and had experience in both types of treatment (fasciectomy and CCH), and they and their aides are responsible for hand surgery of a geographical area in Spain. Only at symposia like the Groningen conference a larger number of experienced specialists in Dupuytren Disease can be found. This paper does not attempt to compare efficacy or results of treatments for Dupuytren Disease. It rather presents a way to help in the decision-making or consensus process. We have selected fasciectomy and CCH because novel and feasible treatments for Dupuytren Disease are well known for this group of clinical experts in hand surgery, thus facilitating understanding of the questions of the survey.

Our work applies to the realization of a first-step survey for the unification of criteria prior to a second-step method (e.g., Delphi, based on the

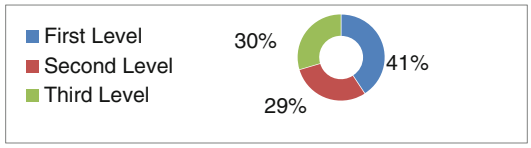

Fig. 37.3 Level of care of the hospital of the orthopedic surgeons

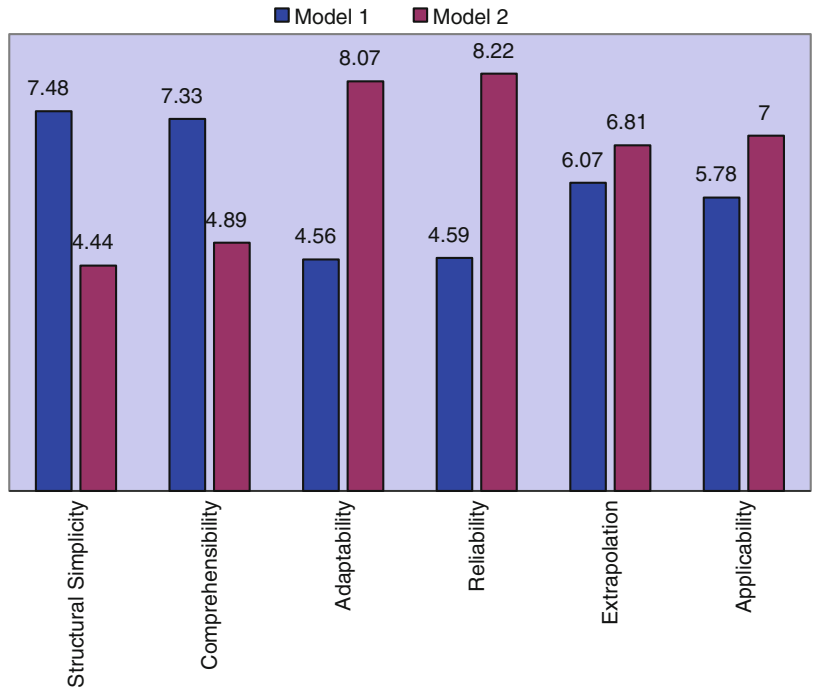

Fig. 37.4 Mean score

preliminary results of the survey). The statistical results show that the proposal is viable for this purpose.

Conclusions

- Our results show that both models studied could be considered equivalent. However, model 2 appears to be more reliable and adaptable than model 1, which is simpler and easier to understand.
- The clinical validation of a pharmacoeconomic model is possible in DC and is a prerequisite for its use in pharmacoeconomic studies.
- The survey of experts is a pharmacoeconomic modeling method that is valid, economical, and whose clinical validation method is feasible, as well as being applicable to other fields of investigation.

Acknowledgments and Declaration of Conflict of Interest We are grateful for the collaboration of the participating surgeons at the *XVII Reunión Interhospitalaria del Grupo de Cirugía de la mano de la Comunidad Valenciana (17th Interhospital Conference on Hand Surgery held in the Region of Valencia),* on Nov. 21, 2014, at the Supress Marina Salud. The affiliation of the hospital is Hospital de Denia.

The authors declare that they have no conflicts of interest.

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Part VIII

Surgical Techniques and Recurrence

Ilse Degreef and Ulrich Lanz,
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38 Preliminary Soft-Tissue Distraction with the Digit Widget™ in the Management of Advanced Dupuytren Contracture at the Proximal Interphalangeal Joint

Solomon Azouz, Atanu Biswas, and Anthony Smith

Contents

38.1 Introduction

Dupuytren Disease results in a progressive shortening of the palmar soft tissues consequently restricting extension at the PIP joint. This limitation of active extension at the PIP joint is subsequent to the shortening of the pretendinous cord(s); checkrein ligament development; contracture of the collateral ligaments, the skin ligaments, and the flexor tendon sheaths; fibrous scar contracture; or a combination of these afflictions (McFarlane 1974; Craft et al. 2011).

Therapeutic interventions are performed for two purposes: firstly, to relieve the limitation of range of motion caused by the flexion contracture and, secondly, to improve active and passive extension at the proximal phalangeal and metacarpophalangeal joints (Agee and Goss 2012). Nonoperative techniques such as serial splinting, casting, enzymatic degradation, and stretching have been historically implemented to allow gradual lengthening of the contracted tissues (Ball and Nanchahal 2002; Messina and Messina 1993; Rives et al. 1992; Citron and Messina 1998; Larocerie-Salgado and Davidson 2012; Brandes et al. 1994). The success of these techniques relied upon the increase in newly synthesized collagen. This new collagen is remodeled and increased due to recruitment of degradative enzymes, metallo-

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proteinases, collagenase, and cathepsins B and L (Brandes et al. 1994). Serial splinting and casting are complicated by dorsal digital skin ischemia, pain, and potential dermal thinning and ulceration (Agee and Goss 2012). The Digit Widget™ (Hand Biomechanics Lab, Inc., Sacramento, CA) was specifically developed for the treatment of severe PIP joint contractures with the avoidance of soft-tissue complications previously associated with serial casting and splinting techniques.

38.2 Methods

38.2.1 Physiological Features of Soft-Tissue Distraction

The Digit Widget™ is a dynamic external fixation device designed to provide an extension torque across the PIP joint for lengthening of the palmar soft tissues in cases of advanced Dupuytren Disease. The force exerted by the Digit Widget™ is directly applied through the digital phalanges thereby eliminating any forces on the dermis. The traction device does not limit flexion. The patient can actively and passively flex the finger with the Digit Widget™ in place by releasing the traction produced by the device. The patient can adjust the extension torque to minimize pain and morbidity.

38.2.2 Indications for Use

The indication for use of the Digit Widget™ is a desire for improved range of motion and the correction of severe PIP joint flexion contractures. In those cases where there is evidence of advanced joint destruction such as in arthritis, or after trauma, the Digit Widget™ may be of limited benefit. Patients with unstable or subluxed PIP joints as a result of long-standing collateral ligamentous injuries are also not suitable candidates for the placement of the Digit Widget™. Any injuries to the pulley system, previous injuries, and previous surgical intervention are all important in the consideration of the use of the Digit Widget™, as these conditions are at the highest risk of recurrent flexion contracture.

38.2.3 Application of the Digit Widget™

In those patients who are appropriate candidates for placement of the Digit Widget™, the device is commonly used for 6 weeks. The Digit Widget can be placed under general anesthesia or with a local or regional block such as an axillary nerve block. The placement of the Digit Widget™ begins with marking the dorsal mid-longitudinal axis of the digit and identification of the PIP joint which is marked under fluoroscopy. The locating drill guide is then placed on the middorsal line just distal to the PIP joint. The locating drill guide is used to place a proximal and distal pre-drill pin under fluoroscopic guidance. These measures are followed to avoid drilling through the joint or to damage the flexor tendons. The distal pre-drill pin is then removed and replaced with a permanent distal screw which is then repeated proximally. After confirmation of permanent screw depth under fluoroscopy, the screw shrouds are cut and the drill guide is removed. The pin block is seated 5 mm above the dorsal skin which accommodates finger swelling.

Over the course of treatment, the Digit Widget™ will gradually stretch the palmar soft tissues, the neurovascular bundle, and the dermis of the affected digit. This will simultaneously reduce the flexion contracture deformity at the PIP joint. The goal of treatment is reducing the flexion deformity by up to 15° per week with full correction of skin and soft tissue by 6 weeks of treatment. If the PIP joint is fully extended and the volar PIP joint skin and soft tissue is supple, the Digit Widget™ is removed and no additional surgery is needed. When the Digit Widget™ therapy plateaus before full extension is achieved, surgery may be required to release the residual contracture (Craft et al. 2011). Additionally, surgery may be required if significant Dupuytren Disease or contracture is present.

The Digit Widget™ when used in tandem with operative correction of Dupuytren contracture yields the best results in correcting advanced cases of PIP flexion contracture (Craft et al. 2011). Prior to placement, the dorsal mid-longitudinal axis of the affected digit is meticulously delineated

(Fig. 38.1). We include a case presentation of a 76-year-old right hand-dominant male with right small finger flexion of 55° at the metacarpophalangeal (MP) joint and right small finger 90° at the PIP joint due to Dupuytren Disease. The patient had no prior surgery (Figs. 38.2, 38.3, 38.4, and 38.5).

38.2.4 Postoperative Considerations

Complications of Digit Widget™ placement are acute or delayed. Acute complications are related to inaccurate placement of the pins leading to iatrogenic middle phalanx fracture or leaving the pins too long causing impingement on the cuff as the contracture improves. Delayed complications are rare but include severe pain or infection and if either does not resolve with treatment may necessitate removal of the Digit Widget™ prior to complete correction.

38.2.5 Management of Applied Torque

Applying the correct amount of torque to the PIP joint is critical to avoid pain, edema, and loss of flexion in the joint. Torque imbalances can also cause MP joint hyperextension due to reduced resting tension in the proximally translocated flexor digitorum superficialis and profundus tendons as well as an increased moment arm due to the dorsal dislocation of the extensor tendon off the metacarpal head. The extension torque on the MP joint caused by PIP joint flexion contractures leads to MP joint hyperextension which reduces the efficiency of the Digit Widget™ (Agee and Goss 2012). The result is a limitation of proximal excursion of the extensor tendon and its central slip. The net effect is inefficient mechanics required for PIP joint extension. Therefore, critical to achieving long-term active PIP joint extension after reversal of contracture is restoring central slip tension and excursion. If one identifies excessive hyperextension in the MP joint, the MP flexion strap can be used to prevent MP joint hyperextension to facilitate rebalancing of torque forces across the MP joint to allow more efficient PIP joint extension. Edema which causes stiffness of the PIP joint can further undermine device effectiveness.

38.2.6 Monitoring Device Efficacy

Patient participation is critical to the success of treatment with the Digit Widget™. Full correction of the PIP joint flexion deformity is achievable by 6 weeks after placement. Patients are carefully followed at weekly intervals; range of

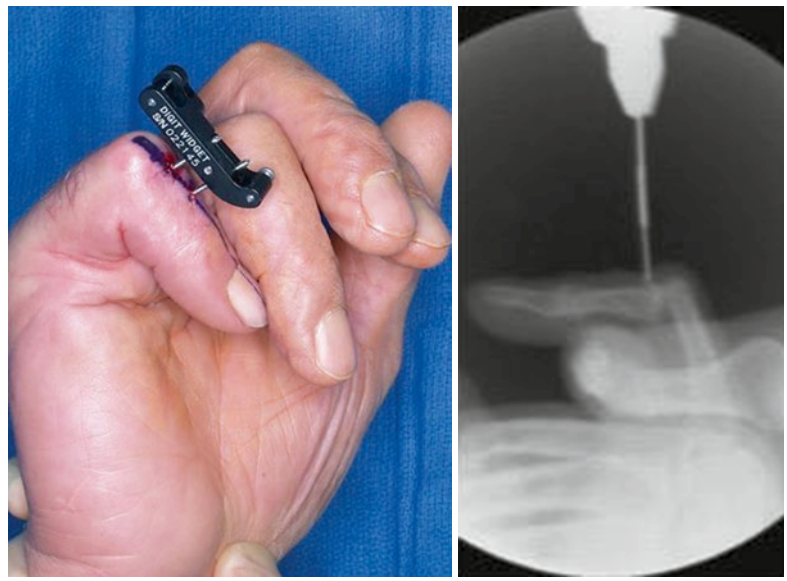

Fig. 38.1 Placement of the Digit Widget™. The Digit Widget™ is placed on the dorsal mid-longitudinal axis. Placement under fluoroscopy assures the device is placed in good position and that pins are not put into the joint.

motion is plotted and rubber bands are adjusted as needed. Progress is plotted as a graph of the change in range of motion as a function of time. Patients are also encouraged to record their progress daily in a "diary." Rubber bands, which include light, medium, and heavy, are changed daily and added if needed. Once 5 bands of the same gauge are used together, a switch to a larger rubber band is made.

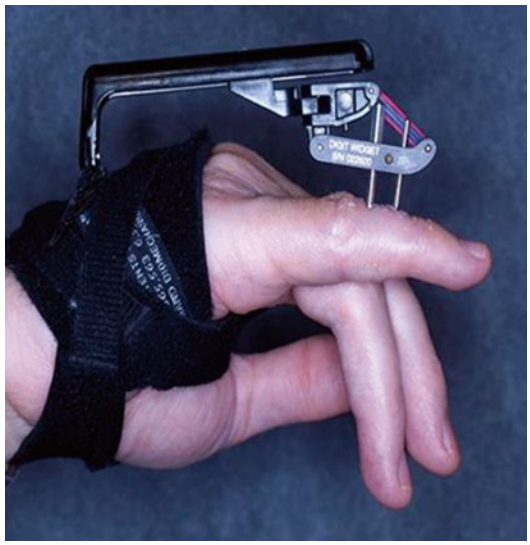

Fig. 38.2 Connector assembly and rubber band placement

38.3 Discussion

The ideal management of severe PIP joint contractures is likely a combination of many treatments, and surgical management of Dupuytren contractures remains a challenge (Donaldson et al. 2010; Misra et al. 2007; Van Giffen et al. 2006). The Digit Widget™ is an important tool to add to the armamentarium of the hand surgeon in treating difficult flexion contractures of the PIP joint.

There has been a limited recorded experience regarding the use of the Digit Widget™ combined with surgery (Craft et al. 2011; Agee and Goss 2012; Bailey et al. 1994). To date, there have been no studies that compare the effectiveness of the Digit Widget™ to dynamic extension splint orthoses.

Many groups have studied various external fixators with and without fasciectomy. Craft et al. demonstrated a statistically significant extension improvement in digits treated with distraction of 53.4° compared to 31.4° in digits treated with fasciectomy plus ligament release (Craft et al. 2011). If avoidance of uncommon complications can be maintained and if there is patient compliance, the Digit Widget™ is extremely effective in advanced contractures.

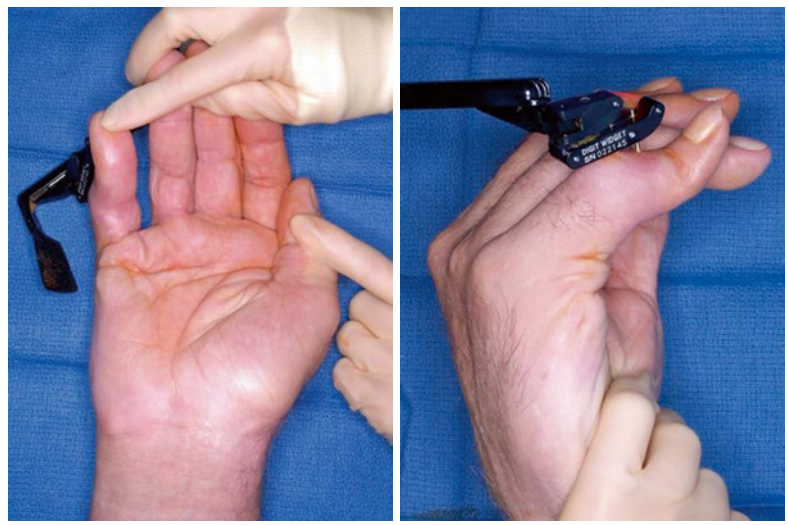

Fig. 38.3 Following 6 weeks of Digit Widget™ application, the patient's PIP contracture is dramatically improved. Though the patient's DIP joint is hyperextended, this improved with the surgical Dupuytren contracture release and postoperative hand therapy. No Fowler distal tenotomy was required

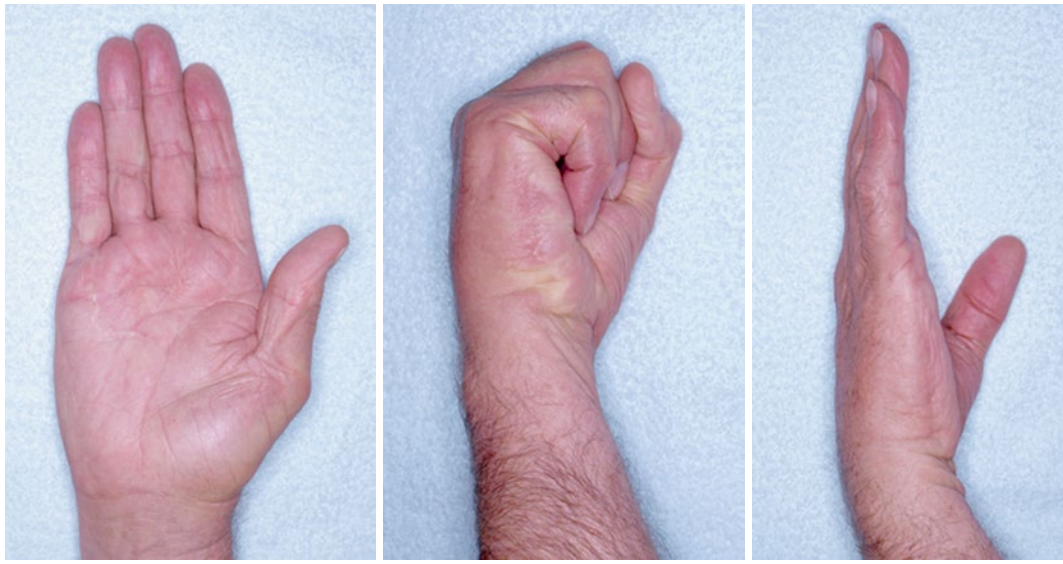

Fig. 38.4 3 months following widget removal and contracture release

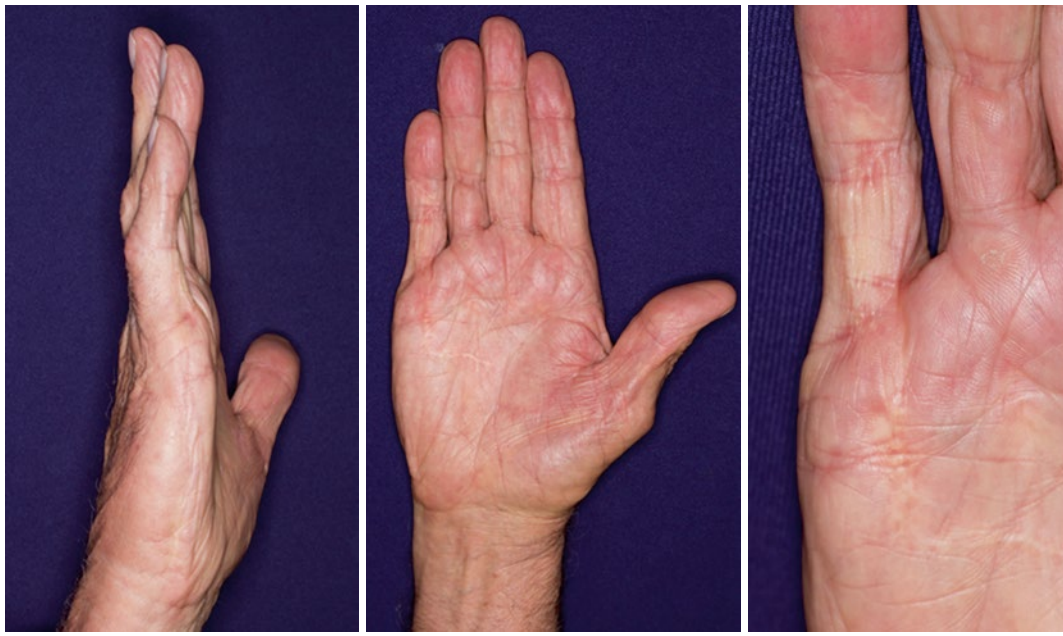

Fig. 38.5 5 years following widget removal and contracture release

Conclusions

- Long-term data on the role of the soft-tissue distraction devices for PIP joint flexion deformities are lacking.
- Preliminary distraction with the Digit Widget™ may be followed by fasciectomy.
- Preliminary data of the Digit Widget™ shows superior extension improvement compared to checkrein ligament release after fasciectomy, with no recurrence in the Digit Widget™ cohort particularly in those with severe disease (>60° contracture of the PIP joint).

- Highly powered studies are needed to characterize recurrence and complications after use of the Digit Widget™.

Conflict of Interest Declaration We do not have any disclosures to declare or conflicts of interest in the completion of this work.

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39 Is Recurrence After Treatment Predictable? Risk Factors in Dupuytren Disease

Maarten Van Nuffel and Ilse Degreef

Contents

39.1 Introduction

Dupuytren Disease (DD) is a connective tissue disorder characterized as nodular palmar fibromatosis, which causes permanent contraction of one or more fingers. In general, these nodules and contractures are not painful but can lead to severe functional impairment. Despite huge amounts of research on the clinical, histopathological and molecular aspects of DD, many aspects of this condition remain unclear.

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39.2 Background

39.2.1 Recurrence

When discussing the predictability of recurrence, one needs a clear definition of recurrence. A distinction needs to be made between an objective recurrence of contracture, as measured by a clinician, and a subjective recurrence, as perceived by the patient. Historically, the objective definition of recurrence was mainly based on disease recurrence in a previously operated field (Hueston 1963a; Gordon 1957; Leclercq 2000). Defining recurrence in different ways has caused a lot of confusion in the literature and makes comparing studies difficult. This also explains the wide range of recurrence rates from 2 to 86 % (Becker and Davis 2010; Kan et al. 2013; Werker et al. 2012). To overcome this problem, an international consensus has been published in 2014 (Felici et al. 2014). Using the Delphi method, an international committee of hand surgeons defined recurrence as a passive extension deficit (PED) of more than 20° for at least one treated joint, in the presence of a palpable cord, compared to the result obtained at time 0. Time 0 was defined as

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the period between 6 weeks and 3 months after treatment and is the time when treatment results can be considered stable. Recurrence needs to be distinguished from extension, which is considered the development of nodules or cords in adjacent fingers or other areas not operated before (Tonkin et al. 1984).

39.2.2 Disability

On the other hand, patients often desire treatment based on their functional impairment, and this is not always correlated to the objective degree of contracture. Professional activities and hobbies may influence the degree to which patients are impaired by the disease and the moment they request treatment of the contractures. In 2009, Degreef et al. (2009a) reported that there seems to be no correlation between the degree of contracture and the disability, as expressed by the DASH score (disability of arm, shoulder and hand). One of the problems is that the DASH score is not specific enough for DD. In 2013 Wilburn et al. demonstrated that DD affects both performance of activities and quality of life, and they expressed the need for DD-specific outcome scales that are valid, reproducible and responsive. In the same year, Ball et al. (2013) published a systematic review on functional outcome measures in DD. They recommended the use of a region-specific questionnaire such as the Michigan Hand Questionnaire (MHQ) and a validated disease-specific patient-related outcome measure like the Unité Rhumatologique des Affections de la Main (URAM) scale (Beaudreuil et al. 2011). They also mentioned that adding the designation of tasks important to each patient would be useful, as well as indicating the degree of difficulty before and after treatment on a linear scale. Lastly, patient's satisfaction should be assessed using a valid and reliable questionnaire or patient evaluation measure.

39.2.3 Rationale

In the past decades, several authors have been searching for the factors that are associated with a high recurrence rate after surgery. For example, if the recurrence risk could be predicted based on these findings, patients with a high recurrence risk would be more frequently splinted and checked after the operation. This is particularly interesting since there is an increasing debate on the usefulness of splinting postoperatively (Collis et al. 2013; Larson and Jerosch-Herold 2008; Jerosch-Herold et al. 2011). Interestingly, in hand rehabilitation after tendon repair, hand therapists seem to classify their patients during the rehabilitation as "scar formers" or "non-scar formers" and may adapt the rehabilitation protocol according to this classification (Pitbladdo and Strauss-Schroeder 2013). If the same could be done in the postoperative period after treatment for DD, recurrence rates after treatment might improve significantly, independent of the type of initial treatment.

39.3 Surgical Factors

There is still a lot of debate about the best surgical procedure for finger contractures in DD, and most techniques have both enthusiastic supporters and opponents. The same is true for less invasive treatment methods such as percutaneous needle aponeurotomy and collagenase injections.

For example, our group published the results of 3 different operations for DD with contracture of the proximal interphalangeal (PIP) joint. Sixteen patients underwent an open fasciectomy, 13 patients underwent a segmental fasciectomy as described by Moermans (Moermans 1991) and 9 underwent a dermofasciectomy with full-thickness graft. At a mean follow-up of 54 months (range 27–75), the type of operation was not related to the recurrence rate. However, the preoperative extension deficit in the PIP joint was significantly correlated with recurrence (van Giffen et al. 2006). Misra et al. published their results in 2007 and demonstrated that the need for joint release was not correlated with recurrence in 49 PIP joints in 37 patients. Again, the severity of the preoperative contracture (more than 60°) and incomplete correction

of the PIP joint contracture were associated with the recurrence at 18 months (Misra et al. 2007). Degreef et al. reported in 2009 on the self-reported recurrence rates in 216 surgically treated patients with a minimal follow-up of 2 years. Surprisingly, the recurrence rate in the four different operative techniques (Z-plasty, Bruner incision, segmental fasciectomy or dermofasciectomy with full-thickness graft) was not significantly different. Moreover, the recurrence rate in the dermofasciectomy with full-thickness graft as a revision procedure was higher than when this was done as a primary procedure (Degreef et al. 2009c). Roush and Stern published similar findings in 2000; they demonstrated that the total active motion (TAM) after dermofasciectomy with full-thickness graft for recurrent DD was no longer different from the preoperative TAM at a 4-year follow-up examination. However, fasciectomy with local flap coverage seemed to be the only technique that still had an improved TAM at the 4-year follow-up (Roush and Stern 2000).

As mentioned before, the self-reported recurrence rate, although a very subjective parameter, cannot be ignored in the evaluation of treatment of DD. Dias and Braybrooke also reported on the self-reported recurrence in an audit in 1177 patients in 2006. A multi-centre postal questionnaire study was conducted by the Audit Committee of the British Society for Surgery of the Hand. With a mean follow-up of 27 months, they found that recurrence was more common in patients with greater initial deformity and less common if adequate correction was achieved at the time of surgery (Dias and Braybrooke 2006). It appears that the immediate postoperative result is more important in preventing recurrence than the surgical technique used to achieve the correction.

The potential benefit of a full-thickness graft remains a subject of debate. In the 1984 study by Tonkin et al., they found an overall recurrence rate of 46.5 % in 229 operations with a mean follow-up of 37.7 months (range 9–90). The recurrence rate was the highest in men who were treated with fasciectomy alone (54 %), although the combination with full-thickness grafting still showed significant recurrence rates, both as a primary procedure (33 %) and as a revision procedure (42 %) (Tonkin et al. 1984). Ullah et al. reported their results in 2009; in 90 fingers, 44 underwent a dermofasciectomy with a so-called "firebreak" skin graft and 46 underwent a fasciectomy. With a mean follow-up of 36 months, they found an overall recurrence rate of 12.2 %, but there was no difference in recurrence rate between the two groups (Ullah et al. 2009). Interestingly, the same patient cohort was reviewed 2 years later, 63 of these patients could be included and there appeared to be 4 types of evolution after the operation, independent of the initial surgery. They differentiated between minimal re-contracture, mild early recurrence, severe early recurrence and progressive re-contracture. Worsening of the contracture more than 6° between 3 and 6 months after surgery seemed to predict a progressive re-contracture at 5 years (Dias et al. 2013).

39.4 Genetics

It appears that there are inherent, patient-related factors that influence the outcome after surgery. It is well known that DD can have a strong familial predisposition, and a lot of research has been done to identify the genes involved (Bayat et al. 2002; Bayat et al. 2003; Hindocha et al. 2006a; Hu et al. 2005). For example, Dolmans et al. reported in 2012 that there were 9 single nucleotide polymorphisms (SNPs) associated with DD in a genome-wide association study. DD patients with clinical diathesis features (predominantly knuckle pads) are more likely to carry more risk alleles for the discovered DD SNPs than patients without these diathesis features (Dolmans et al. 2012).

A detailed description of the genetic factors in DD falls outside of the scope of this chapter. However, the knowledge of these genetic factors might give us more insight in predicting recurrence, especially since the expression patterns of these genes can be evaluated on histological examination.

39.5 Histopathology

The idea of using histopathology to identify patients at risk for recurrence is not new, but it is still unclear if the underlying process is an inflammatory process or a neoplasm (Wang and Zhu 2006). This makes the development of histological classification more troublesome. Already in 1959, Luck described different histological stages of DD, namely, "cell-rich" proliferation and involution stages versus residual "cell-poor" stages. The latter is supposed to be correlated with a less-active disease (Luck 1959). Rombouts et al. also examined a correlation between histological classification and recurrence. They described 3 types of histology obtained during fasciectomy in 77 hands of 63 patients. The proliferative type had a high cellularity and mitosis rate, and the fibrocellular type showed a prominent reticulin network, whereas the third or fibrous type contained only few cells. The recurrence rate in patients with type 1 was 70 % versus 18 % in type 3 patients at a mean follow-up of 5 years (range 2–10) (Rombouts et al. 1989).

Since gene expression can be examined in harvested tissue, the expression patterns of earlier identified genes can be evaluated histologically. Johnston et al. described the matrix metalloproteinase (MMP) expression in DD and its correlation with clinical outcome in 2008. In 19 tissue samples obtained in simple fasciectomy and with a mean clinical follow-up of 14 months, they found a considerable correlation between levels of gene expression of several of the MMPs (2, 13, 14, 16,19) and "a disintegrin and metalloproteinase with thrombospondin motifs" (ADAMTSs 2, 4, 5, 14, 16) and the recurrence of fixed-flexion deformity. Two genes showed a negative correlation. Not surprisingly, these were tissue inhibitors of metalloproteinases: TIMPs 3 and 4. The authors postulate that knowledge of these expression levels could be used to direct appropriate surgical and adjuvant intervention for DD.

At our own institution (Johnston et al. 2008), we researched the expression pattern of beta-catenin in DD tissue of 12 randomly selected tissue samples of patients with a recurrence at a minimal follow-up of 3 years and in 11 tissue samples from patients without recurrence at that time. We could not find a correlation between the expression pattern and disease recurrence. However, the clinical parameters of these patients were also recorded, and these did show a correlation with recurrence (Degreef et al. 2009b).

39.6 Clinical Parameters

As shown by the study of Dias et al. in 2013, different recurrence patterns seem to exist, independent of the surgical procedure. This knowledge has been around for decades. In the book by Hueston and Tubiana on DD, Dupuytren diathesis was already mentioned, and a list of several risk factors for recurrence and/or extension of the disease was given. These included bilateral disease, early onset, a positive family history and involvement of other areas than the hand. When all factors were present, the extension or recurrence rate was 78 %, but when all factors were absent, the rate was only 17 % (Hueston 1963b). The term "diathesis" describes a condition, constitution or morbid habit that would predispose an individual to a particular disease. The past few years, this concept has been broadened to "fibrosis diathesis", since many patients with DD show signs of fibrosis outside of the hand. Among these, lesions on the plantar side of the feet (Ledderhose Disease) and on the penis (Peyronie disease) are well known. However, Garrod nodules or knuckle pads are also frequently associated. Some authors even suspect a correlation with frozen shoulder syndrome, since one study showed that DD was 8 times as common in patients with frozen shoulder as in the general population (Smith et al. 2001).

To facilitate this risk evaluation, Abe et al. designed a score based on these risk factors. They combined risk factors with a high sensitivity and a low specificity (bilateral disease and 5th finger surgery) with risk factors with a low sensitivity but a high specificity (early onset, plantar fibrosis, knuckle pads and radial side involvement). Based on their calculations, plantar fibrosis, knuckle pads and radial side seemed to have more importance and were awarded 2 points each. The other risk factors each count for

one point. Adding up these 6 variables results in a score between 0 and 9. A diathesis score of more than 4 is associated with a high risk of recurrence, whereas there is little risk of recurrence and extension with a score of less than 4 (Abe et al. 2004).

Discussion still exists on the influence of gender. In the 1984 study by Tonkin et al., the women in their group of 128 operations in 100 patients showed a lower rate of recurrence and a slightly lower rate of disease extension (Tonkin et al. 1984). Similar findings were reported by Wilbrand et al. in 1999. Of 2375 operations in 1600 patients, 14.5 % were performed on women. The mean age at first operation was later in women (62.4 years versus 59.8 in men), and the reoperation rate was 1/4 in women versus 1/3 in men. On the other hand, Anwar et al. published their findings in 2007 on 119 hands in 109 women, compared to 548 men. At a mean follow-up of 12 months, they saw a recurrence rate of 22 %, and final contracture correction, recurrence and complication rates were statistically similar to men (Anwar et al . 2007). In our own institution, we reviewed 65 women with a mean follow-up of 7 years and 7 months (2y1m to 21y9m). There was a 42 % recurrence rate in this group, and the same risk factors were present: a high family history occurrence, bilateral disease and associated Ledderhose Disease. Interestingly, 45 % of these patients had a confirmed diagnosis of frozen shoulder (Degreef et al. 2008).

These risk factors were further clarified by Hindocha et al. in 2006, based on their findings in 322 patients with a minimum follow-up of 4 years and an overall recurrence of 44 %. They defined as positive a family history as a 1st or 2nd degree relative and early onset as an age of onset younger than 50 years. Apart from these, they found that male gender, bilateral disease and ectopic lesions (including knuckle pads) were independent risk factors. In their series, a combination of these 5 risk factors gave a predictive recurrence risk of 71 % versus 23 % without them (Hindocha et al. 2006b).

This was researched in our department as well, using the self-reported recurrence in 342 patients with a minimal follow-up of 2 years. Correlated risk factors were age of onset under 50 years, bilateral disease, Ledderhose Disease, first ray involvement, multiple ray involvement, ectopic fibromatosis, family occurrence and male gender. Recurrence in women was 42 % versus 58 % in men. The time to recurrence was approximately 5 times shorter for males than for females. The Abe score was calculated and correlated well with disease recurrence ($p = 0.004$). As shown in the other studies, the cumulative presence of different risk factors increased the recurrence rate. Although other factors appear to be related with the occurrence of Dupuytren Disease, like smoking, epilepsy, frozen shoulder and diabetes, no relation was found with the aggressiveness or the postoperative recurrence of the disease. This indicates that these disorders may very well induce a Dupuytren-like disorder, but are not necessarily related to Dupuytren diathesis with an aggressive form and high recurrence rates (Degreef and De Smet 2011).

Almost all this research has been done concerning recurrence after surgical treatment. It remains unclear if the same factors are correlated with recurrence after collagenase injections. Some early reports could not confirm these findings in patients treated with collagenase. Kaplan et al. presented their results at the FESSH meeting in 2015 on 1081 joints treated in 644 patients with a recurrence rate of 47 % over a 5-year period. The only variables that were associated with greater recurrence were baseline total contracture index (the sum of fixed-flexion contractures of 16 finger joints), bilateral disease, prior surgery, alcohol consumption, low weight and low body mass index (Kaplan et al. 2015). We recently reviewed the outcome of collagenase injections in our institutions, recorded the possible risk factors and calculated the Abe score, but were unable to find a correlation between the Abe score or individual risk factors and recurrence (Cootjans et al. 2015, unpublished data). Further research will give us more insight in these possible correlations.

Conclusion

Although recurrence in an individual patient can never be predicted 100 % accurately, there are some factors that allow us to estimate the

risk. The initial deformity before the operation and the result immediately after surgery are important factors. Apart from these, the fibrosis diathesis can serve as a guideline in predicting recurrence risk. Since no technical investigation has shown to be adequately useful for prediction, clinical parameters should be used to categorize the disease in benign forms versus severe diathesis. In the first group, early recurrence is unlikely and probably one procedure will resolve the problem. Recurrence is to be expected only on the long term and may not necessarily need re-intervention. In patients with a severe fibrosis diathesis, however, almost certainly several procedures will be necessary, as well as a more aggressive postoperative regime and maybe even adjuvant treatment.

Conflict of Interest Declaration Nothing to declare.

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Is Recurrence of Dupuytren Disease Avoided in Full-Thickness Grafting?

40

Ilse Degreef and Marieke Torrekens

Contents

40.1 Introduction

In Dupuytren Disease, finger contractures are the main reason for treatment. At this moment, only the symptoms, the contractures, can be addressed; there is no cure for the disease. Minimal invasive treatment allows for quick recovery and low morbidity. More extensive surgical techniques mostly aim for complete removal of macroscopically affected tissue (fibroproliferative nodules and cords). Evidently, longer incapacity and extended rehabilitation periods are inevitable.

The preference of treatment options depends on different factors. First, there is the doctor's/surgeon's preference and experience or training. Next, the patient's choice will influence decision-making: he may prefer quick recovery to extensile surgery. And last, technical issues will steer treatment options. In case of joint contractures, minimal invasive surgery may not be feasible; in case of severe skin involvement and shortage, skin grafting may be required if Z-plasty would not cover defects sufficiently and self-healing is not preferred, although acceptable outcome of open palm techniques has been reported (McCash 1964).

When Hueston introduced full-thickness skin grafting in extensive debridement with skin excision in Dupuytren surgery (dermofasciectomy, also known as subtotal preaxial amputation) in 1984, he mentioned the 'firebreak' capacity of his technique. Based on the

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observation of non-recurrence of Dupuytren tissue underneath full-thickness skin grafts, he suggested 'firebreak' graft areas between areas of potential flare-up (Hueston 1984).

In this chapter, the authors reviewed scientific background on skin involvement in Dupuytren Disease, the clinical impact and the reported and experienced results. We aim to define the role of full-thickness graft treatment strategy in today's treatment algorithm for Dupuytren Disease.

40.2 Choice of Surgery

Numerous surgical techniques have been introduced over the past decades. Incisions vary in length, form and direction. Basically, treatment options in contracture release can be categorised based on increasing invasiveness or extensile properties. Minimal invasive techniques as needle fasciotomy focus on fasciotomy, simply interrupting the cords. The fasciotomy is slightly extended in enzymatic fasciotomy (collagenase injections) or partial cord resections as in Moermans' segmental fasciectomy. The total cord can be removed (fasciectomy) and in extended surgery, the overlying skin as well (dermofasciectomy). In the latter surgical option, the wound can be left open (as is also applied in Open palm technique (McCash, 1964), although not at random) or covered with full-thickness grafting (Hueston 1982).

As mentioned earlier, the choice is based on individual preference of patient and surgeon and on technical necessities (skin involvement and shortage). However, often surgical technique is chosen by motivation of full resection of all macroscopically affected tissue. Both surgeon and patient are motivated to opt for extensive surgery to prevent recurrence. This is based on tumour hypotheses: tumour removal in toto should cure the disease; incomplete resection would be prone to recurrent fibroproliferative growth. However, both clinical and basic research increasingly support the idea of a chronic inflammatory-like process, instead of tumour-like tissue: complete resection is not required and does not guarantee indefinite results. The fibroproliferative tissue may recur at any given moment, even in extensile debridement (similar to inflammatory responses to unknown stimuli). Patients with high fibrosis diathesis are prone to recurrence (Geoghean et al. 2004; Abe et al. 2004).

Therefore, minimal invasive surgery may always be considered, if feasible, to shorten rehabilitation time and increase comfort (Degreef et al. 2009). Extensive surgery is prone to complications and should be considered carefully, outweighing risks and benefits (Bulstrode et al. 2005).

However, the only standing hypothesis, which may rectify more invasive surgery for reasons of recurrence, is full-thickness grafting. Here, we can find reports on series with hardly any recurrence (as opposed to other surgical techniques) underneath the skin grafts (extension of the disease, away from the grafts, is not lower than any other technique). This localised absence of recurrence is remarkable and may give information on the pathology and influence treatment algorithms.

40.3 Firebreak Principle

In cord interruption surgery, new scar tissue formation bridging the removed fibroproliferative parts may induce recurrent contractures. Certainly in small cord interruptions as in minimal invasive surgery as segmental fasciectomy, inert absorbable blocking implants as, for instance, cellulose have demonstrated their efficiency in improving surgical outcome (Degreef et al. 2011).

If full-thickness grafting carries the same effect of firebreak interruption blocking new cord formation with re-contractures, this could shift preference for this more extensive surgery not only for technically motivated reasons as skin shortage but also more in selected case with, for instance, high-recurrence risk.

Not only the clinical outcome but also the underlying pathological reason for the firebreak effect is intriguing to both the surgeon and the scientist.

40.4 The Skin in Dupuytren Disease

The question arises as to why the skin grafts prevent cords from regrowing to induce contractures and to why new nodules are hardly ever

encountered underneath skin grafts in Dupuytren Disease. Does this mean that the removed skin is involved in inducing or maintaining the fibroproliferative process in Dupuytren Disease? Is all skin then involved or only retracted skin, as we have encountered in our immune-histochemical research on the myofibroblast in Dupuytren Disease? We have seen that in retracted skin (pits), the myofibroblasts are aligned and attached to the superficial skin layers (Fig. 40.1a). In contrast, more loose skin overlying nodules does not seem to be attached to the underlying myofibroblasts (Fig. 40.1b). McCann reported on myofibroblasts extending into the dermis of patients with Dupuytren skin resection and in a minority of the patients into the epidermis. They suggested that this might play an important role in recurrent disease after fasciectomy (McCann et al. 1993). Likewise, Chen et al. reported on the clear presence of myofibroblasts in the skin and subcutaneous tissue of patients who underwent skin resection and grafting by using electron microscopy (Chen et al. 2009). Perhaps this points to the impossibility of isolation of the fibrous tissue from the skin in certain cases. It may also explain part of the success of cellulose implantation, where the skin is isolated from the underlying cord ends after segmental fasciectomy. On top, removing the skin may also add to the efficiency of skin resection without replacement, inducing secondary healing (as in the Open palm technique (McCash, 1964).

On the other hand, it may very well be that the transplantation of full-thickness grafts, coming from the more proximal arm usually, may have different epidermal properties than the skin in the palm of the hand. Perhaps this remote skin holds less or no fibroproliferative-inducing elements in the palm of the hand.

40.5 Subtotal Preaxial Amputation of Hueston

Most naturally, surgical resection of all macroscopically affected contracting tissue in Dupuytren Disease, including overlying skin, is extensive surgery. The challenge is an anatomical dissection of the hand, wherein neurovascular bundles need to be isolated from the fibroproliferative tissue and tendons; pulleys, joints and capsul need to be kept intact. In fact, usually, the palmar preaxial part of the finger is removed leaving a large wound behind, which was the inspiration to name the Hueston technique a subtotal preaxial amputation. Certainly, if the grafting is preferred for reasons of non-recurrence underneath the grafts and firebreak effects, more extensive grafting may be required to maximise Dupuytren-free areas.

40.6 Recurrence in Full-Thickness Grafting

In our department, full-thickness grafting has been performed for over 15 years in Dupuytren Disease. However, it was mostly considered in case of severe contractures with skin shortage or severe recurrent disease (47% had previous surgery with recurrent contractures). We prefer medial forearm skin as donor site providing abundance, hair-free skin and causing hardly any morbidity (Fig. 40.2). Recently, patients were invited for review to evaluate long-term follow-up to assess recurrence or extension of Dupuytren Disease after skin grafting. In a group of 47 patients with a 3–16-year follow-up, not one recurrent nodule or cord was noted underneath the full-thickness skin grafts. However, extension of the disease in adjacent areas was seen in over 4 in 5 patients. Most of these patients with disease extension had a high fibrosis diathesis (detailed report under review) as there was a significantly higher score of Abe for Dupuytren diathesis in the recurrent (extended) group of over 4, where it was under 4 in the group without evidence for recurrent disease and/or contractures (Abe et al. 2004).

On the other hand, during the last three decades, all reports on full-thickness grafting have been promising. Presumably it is the extensiveness of the procedure and the vast recovery period that prevent patients and surgeons from choosing this procedure as the first standard in most hand practices.

In 1992, Kelly and Varian saw 2 recurrences in 24 patients, but extension of the disease was seen in almost half of them (Kelly and Varian 1992). In the same year, Searle and Logan observed minimal nodule formation at the graft

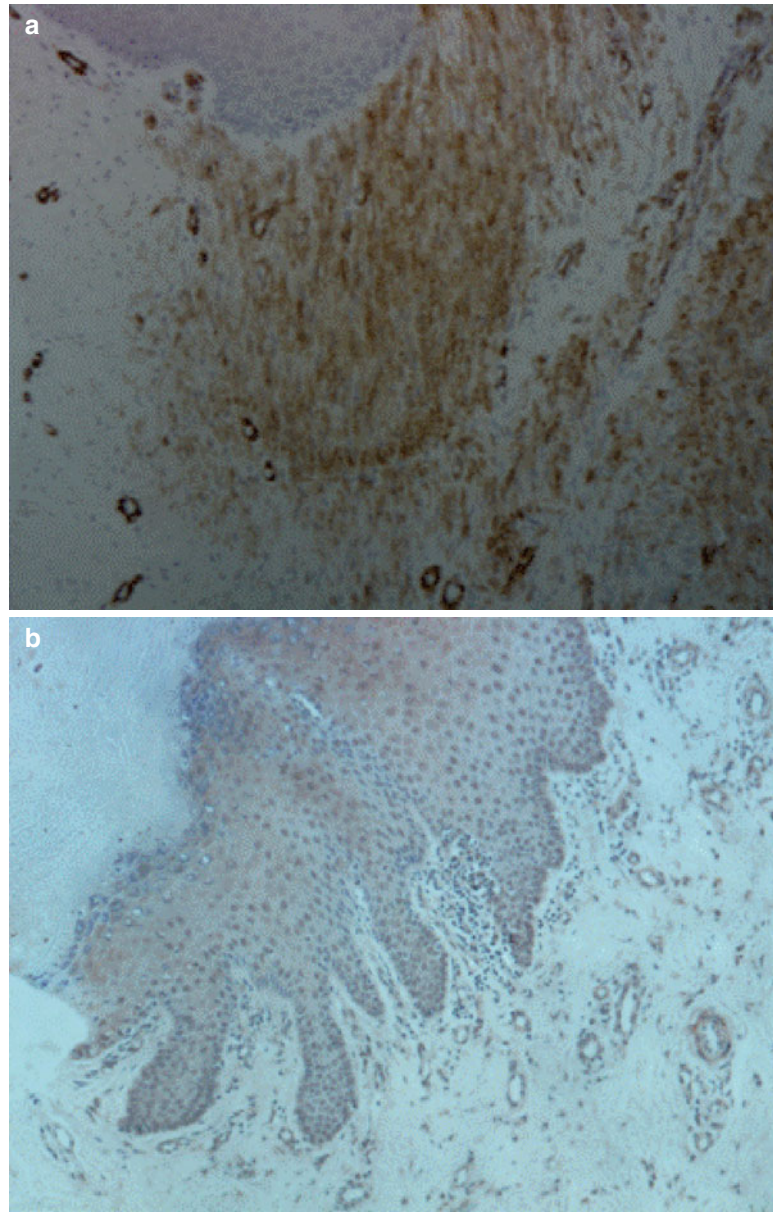

Fig. 40.1 (**a**) Retracted skin in Dupuytren Disease, wherein myofibroblasts are aligned and anchored to the epidermis (brown staining, Alfa smooth muscle actin stained); (**b**) in contrast, the noninvolved skin over a Dupuytren nodule shows no myofibroblasts adhered to the dermis

edges in 4 of 32 patients after 2 years (Searle and Logan 1992). Brotherston et al. saw no recurrence in 34 patients after 5–8-year follow-up (Brotherston et al. 1994). Hall reported 8 % recurrence in 67 patients in 2–7-year follow-up (Hall et al. 1997). Armstrong reported on a low recurrence rate of 11 % in a series of 103 patients after almost 6 years of follow-up (Armstrong et al. 2000). In 2009, Chen et al. again reported no recurrence in 68 patients with full-thickness grafting in contrast to 46 % recurrence in partial fasciectomy (Chen et al. 2009).

In recurrent disease, the decision for full-thickness grafting is easier to make, since disappointment may lead to choosing more daring surgery. And even in recurrent disease, promising reports on outcome of full-thickness grafting are

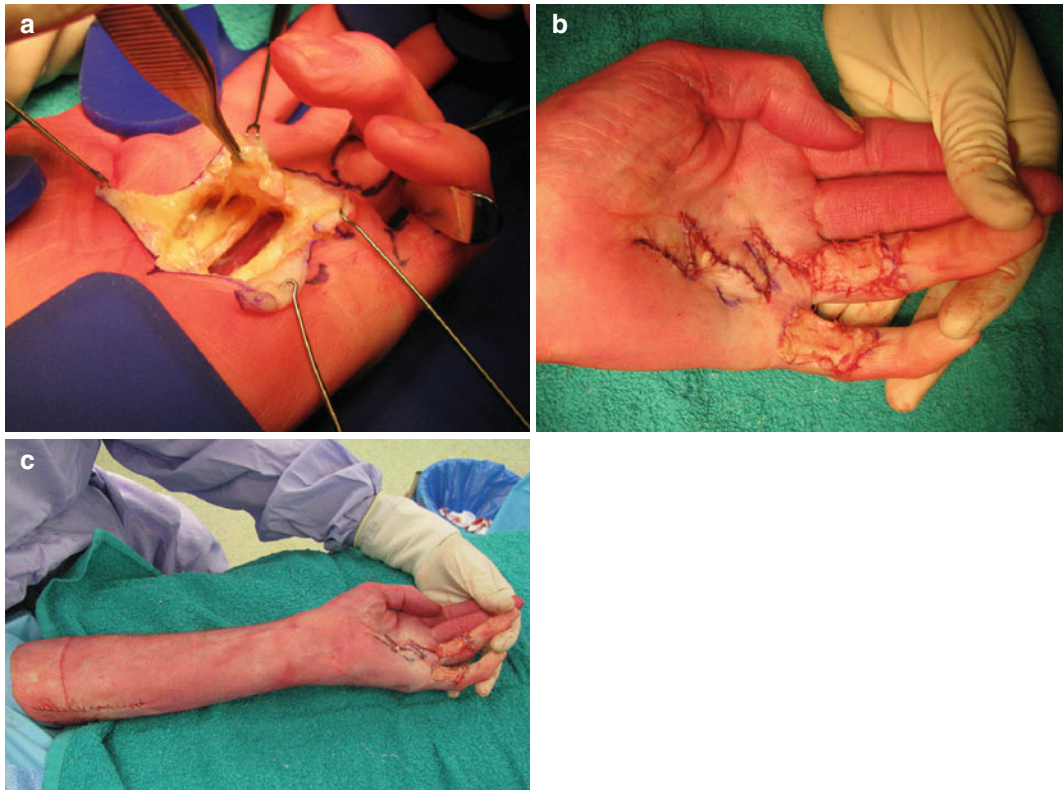

Fig. 40.2 Dermofasciectomy (**a**) and full-thickness grafting (**b**) harvested from the medial forearm (**c**) for recurrent Dupuytren Disease after segmental fasciectomy with hooked deformity in 4th and 5th digits

available. For instance, Abe reported no recurrence in a small series of Japanese patients with recurrent Dupuytren Disease and high fibrosis diathesis, which inspired him to advise full-thickness grafting in severe recurrent disease (Abe et al. 2007). Recently, Villani et al. confirmed good results after a long follow-up of almost 9 years in 18 patients with bilateral recurrent disease and high fibrosis diathesis, with recurrence in 13 % as compared to a 100 % recurrence in the hands without skin graft (Villani et al. 2009).

However, controversy remains. Roush and Stern stated that in their series of 19 nonrandomised patients, dermofasciectomy and full-thickness skin grafting did not prevent recurrent contracture and local flaps had a better outcome (Roush and Stern 2000). In 2009, even a randomised trial in 79 patients could not confirm an improved outcome or rather a decreased recurrence in 'firebreak' full-thickness grafting, with minimal recurrence in 12 % (Ullah et al. 2009). Even Hueston encountered recurrence 5 years after his initial successes, but hypothesised this to be due to deeply localised tissue underneath the neurovascular bundles, which lacks contact with the grafted skin, which he believed to be utterly inhibitive to myofibroblast proliferation (Varian and Hueston 1990).

Conclusions

Although extensive resection of Dupuytren fascia and overlying skin with full-thickness grafting is a major hand surgery with a long recovery time, there are important arguments on its firebreak advantages with lower recurrence of nodules and contractures underneath the graft. Therefore, certainly in high fibrosis diathesis, skin retraction and recurrent disease, full-thickness skin grafting is considered a viable surgical option in severe Dupuytren Disease.

Conflict of Interest Declaration No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this mono-centre article, which is of academic interest only.

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The Use of Acellular Dermal Matrix in Dupuytren Disease

41

Gloria R. Sue and Deepak Narayan

Contents

41.1 Introduction

Dupuytren Disease is a progressive condition that involves abnormal thickening and contraction of the palmar fascia. There is a wide spectrum of clinical presentation. The symptomatic aspect of the disease ranges from isolated palmar pits and nodules to disabling flexion contractures of the metacarpophalangeal and interphalangeal joints.

Surgery has been the traditional mainstay of treatment for symptomatic Dupuytren Disease since the 1800s. Surgical treatment options include fasciotomy (Dupuytren 1834; Luck 1959), fasciectomy (Hamlin 1952), and dermofasciectomy (Hueston 1984). These open surgical procedures are effective in treating disease contracture in the short term. However, disease recurrence has remained a significant problem following surgical treatment. One recent study reported a 39 % recurrence rate following fasciectomy and a 62 % recurrence rate following fasciotomy at a median follow-up of 4 years following surgery (Crean et al. 2011).

Percutaneous treatment options are also utilized to treat Dupuytren Disease. These include percutaneous needle fasciotomy, which involves using a needle to puncture and weaken diseased cords (Rowley et al. 1984). The advantage of this approach is that it is minimally invasive and can be performed in the clinical setting. A more recently developed technique is the enzymatic fasciotomy, which involves injection of collagenase to weaken cords (Watt et al. 2010). While these are attractive alternatives to surgery for the treatment of Dupuytren Disease, these methods are also associated with high recurrence rates following treatment (van Rijssen et al. 2012; Peimer et al. 2013).

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Dermofasciectomy was advocated for the treatment of Dupuytren Disease by Hueston in 1962 (Hueston 1962). This surgical approach involves excision of overlying skin in addition to excision of diseased fascia, followed by the placement of a full-thickness skin graft to the resulting wound bed. He noted that none of these patients had a disease recurrence. Several case series have since corroborated Hueston's observation that recurrence rarely occurs below a skin graft (Heuston 1969; Tonkin et al. 1984; Logan et al. 1985; Ketchum and Hixson 1987; Kelly et al. 1992; Searle and Logan 1992; Brotherston et al. 1994; Hall et al. 1997; Armstrong et al. 2000; Abe et al. 2007). The mechanism underlying decreased recurrence in the setting of dermofasciectomy is poorly understood. One hypothesis is that full-thickness skin grafts are able to decrease activity of myofibroblasts, as suggested by Rudolph (Rudolph 1979). Despite the favorable long-term outcomes associated with dermofasciectomy, it remains an infrequently performed procedure given its significant surgical morbidity.

Given the success of full-thickness skin grafting, we proposed that the use of acellular dermal matrix in the setting of open fasciectomy for Dupuytren Disease could potentially reduce disease recurrence. Our hypothesis is borne out of basic science experiments demonstrating in a primate model that the placement of a sheet of acellular dermal matrix adjacent to an implant minimizes capsule formation and significantly decreases the presence of myofibroblasts compared to controls without acellular dermal matrix (Stump et al. 2009).

41.2 Materials and Methods

We performed a retrospective cohort study of 43 patients undergoing open fasciectomy for Dupuytren Disease from 2005 to 2012. All procedures were performed by a single surgeon (D.N.) at hospitals affiliated with Yale University School of Medicine. Inclusion criteria included patients with symptomatic Dupuytren Disease and presence of nodules and/or contractures (Fig. 41.1). The fasciectomies were performed in a standard fashion via Bruner incisions in all patients. Our intervention involved the placement of a sheet of acellular dermal matrix (Alloderm, LifeCell, Bridgewater, NJ) in the wound bed following the fasciectomy, placed just prior to skin closure. The sheet of acellular dermal matrix was cut to fit the size of the wound bed (Fig. 41.2) and subsequently sutured in with interrupted absorbable sutures. Sequential patients presenting between the years of 2005 and 2007 were included in the control group. Patients presenting between 2008 and 2012 had acellular dermal matrix placed following standard fasciectomy. All patients were evaluated at period follow-up visits in clinic. Disease recurrence was assessed at follow-up. Recurrence was defined as the presence of Dupuytren tissue in an area that was previously

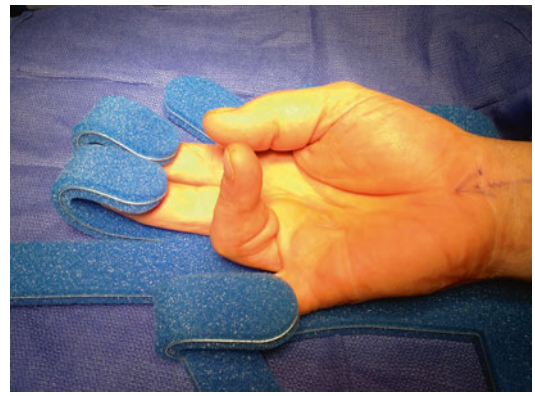

Fig. 41.1 Patient with symptomatic Dupuytren Disease, preoperative

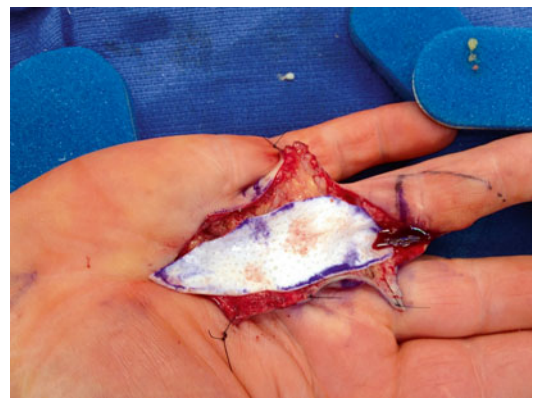

Fig. 41.2 Intraoperative placement of a sheet of acellular dermal matrix in wound bed following standard fasciectomy in the same patient from Fig. 41.1; postoperatively, the finger was completely straightened

operated on, with a contracture greater than that was recorded immediately following the initial surgical procedure.

Patient demographic information was collected for all patients. Additionally, severity of disease, recurrence of disease, wound complications, and other medical comorbidities were recorded. Bivariate analyses were performed using χ^2 analysis using IBM SPSS Statistics version 19.0.0 (IBM, Armonk, NY).

41.3 Results

Our study included 23 patients in the group treated with acellular dermal matrix at the time of open fasciectomy as well as 20 patients in the control group treated only with standard fasciectomy. The median age of the entire patient cohort was 66.5 years (range 54 to 91). There were no statistically significant differences between the two patient groups in terms of age, length of follow-up, severity of disease on initial presentation, presence of diabetes or prostate cancer, use of beta-blockers or alcohol, and presence of seizure disorder (Table 41.1). The locations of disease were also comparable between these two groups (Table 41.2).

We observed a median follow-up of 1.8 years. During the follow-up period, recurrence of disease was observed in 5 of 20 patients (25.0 %) in the control group. In contrast, recurrence was only noted in 1 of 23 patients (4.3 %) in the group with acellular dermal matrix placed. The difference in recurrence rates between these two groups was statistically significant ($P = 0.045$) (Fig. 41.3).

Table 41.1 Characteristics of control and acellular dermal matrix patient cohorts

Characteristic	Control group ($n = 20$)	Dermal matrix group ($n = 23$)
Median age	66	69
Diabetes	5	4
Prostate cancer	8	8
Beta-blockers	3	7
Significant alcohol history	7	9
History of seizure disorder	1	2

Three patients in each group had minor wound complications following surgery. These wound complications all healed with local wound care. We also noted that, interestingly, two patients in the group with acellular dermal matrix placement were noted to have disease extension beyond the border of the acellular dermal matrix, but had no clinical evident recurrence under the area covered by the acellular dermal matrix.

41.4 Discussion

In this study, we propose a novel modification to the standard open fasciectomy for the treatment of Dupuytren Disease. We demonstrate that

Table 41.2 The distribution of affected areas of the hand is similar between the two groups

Affected part of the hand	Control group	Dermal matrix group
Small finger	11	11
Ring finger	14	15
Middle finger	5	7
Index finger	1	1
Thumb	0	2
Palm	8	9

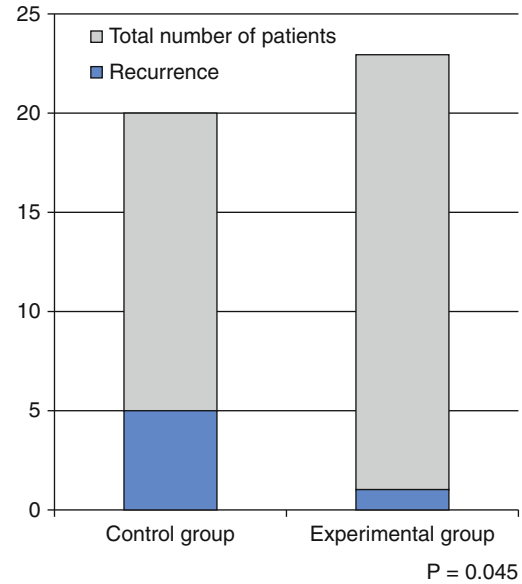

Fig. 41.3 The recurrence of disease was 25 % in the control group compared to 4.3 % in the group with acellular dermal matrix placed

recurrence rates are lower in patients who have a sheet of acellular dermal matrix placed in the wound bed following fasciectomy compared to patients treated with standard fasciectomy for Dupuytren Disease. We observed comparable complication rates between these two groups of patients. Our results have implications for the treatment of Dupuytren Disease.

Currently, no ideal treatment modality exists for Dupuytren Disease. Surgical treatment options such as the standard fasciotomies and fasciectomies are associated with high recurrence rates (Crean et al. 2011). Percutaneous fasciotomies are also associated with high rates of disease recurrence (van Rijssen et al. 2012). Treatment with collagenase injections is also associated with high recurrence rates, with a reported 75 % recurrence rate at eight years following initial injection (Watt et al. 2010). Additionally, up to 100 % of patients receiving collagenase injection for therapy experience at least one treatment-related adverse event, compared to only 21 % of patients undergoing placebo injection (Hurst et al. 2009; Gilpin et al. 2010).

Hueston observed in 1962 that recurrence did not occur in a series of patients undergoing dermofasciectomy for the treatment of Dupuytren Disease (Hueston 1962). In 1969, he reported on a larger series of 65 dermofasciectomy procedures, performed for both primary and recurrent Dupuytren Disease (Heuston 1969). In the follow-up of these patients, he noted that though a few cases of disease extension occurred, there was no recurrence of disease in the areas directly beneath the skin grafts that were placed (Heuston 1969). Since Hueston's studies, several case series have verified his finding of decreased disease recurrence in the setting of dermofasciectomy, with an overall recurrence rate of 4 % from 9 retrospective studies (Tonkin et al. 1984; Logan et al. 1985; Ketchum and Hixson 1987; Kelly et al. 1992; Searle and Logan 1992; Brotherston et al. 1994; Hall et al. 1997; Armstrong et al. 2000; Abe et al. 2007). Despite the effectiveness of dermofasciectomy in treating Dupuytren Disease and in limiting its recurrence, its role in treatment remains limited. The primary reason for this is its significant morbidity secondary to the need for full-thickness skin grafting.

We postulated that the placement of a barrier between the wound bed and the overlying dermis following excision of diseased fascia could recreate the success that Hueston observed in his initial series. The barrier material could theoretically assume the role of a full-thickness skin graft in minimizing subsequent recurrence. We chose to utilize acellular dermal matrix as our barrier material. The rationale behind this selection was based on the increasing popularity of its use in the field of plastic and reconstructive surgery without major complications, reflecting its favorable safety profile. Additionally, histologic studies have demonstrated that its use is associated with decreased proliferation of surrounding myofibroblasts (Stump et al. 2009), which would theoretically be a favorable milieu for patients with Dupuytren Disease, given the central role of myofibroblasts in mediating contracture. We utilized Alloderm, which is an acellular dermal matrix derived from human cadaver skin, treated to remove all cellular and immunogenic components. It retains the structural components of human skin and therefore does not have to be cross-linked, unlike some other dermal matrices, which minimizes unfavorable wound reactions as well as myofibroblast differentiation (van der Veen et al. 2010).

We observed a significantly decreased recurrence rate of 4 % in patients with Alloderm placed in the wound bed following fasciectomy, compared to a recurrence rate of 25 % in patients undergoing the standard fasciectomy. This difference was not attributable to patient-level demographic factors or comorbidities. Interestingly, our 4 % recurrence rate in patients with Alloderm placement identically matches the overall pooled recurrence rate following dermofasciectomy from the retrospective case series. This is a significant finding and has implications for the treatment of Dupuytren Disease, given the ongoing lack of a clear best treatment mechanism. One limitation of our study is our limited sample size. A larger patient cohort would better

elucidate the effect size of the use of Alloderm in reducing disease recurrence. A longer follow-up period would also better demonstrate the effect of our novel intervention.

Conclusions

- Dermofasciectomy is an effective treatment for Dupuytren Disease and is associated with a low recurrence rate of approximately 4 %; however, it is a morbid procedure.
- Patients undergoing open fasciectomy with placement of acellular dermal matrix had dramatically lower recurrence rates compared to patients undergoing open fasciectomy alone (4 % vs. 25 %, $P = 0.045$).

Conflict of Interest Declaration The authors have no disclosures.

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42 Indications of the Continuous Extension Technique (TEC) for Severe Dupuytren Disease and Recurrences

Jane C. Messina and Antonino Messina

Contents

42.1 Introduction

The treatment and knowledge of Dupuytren Disease has evolved in the last few years and has become widely known. Treatment is now performed with techniques as fasciotomy (Dupuytren 1831); needle aponeurotomy (Cheng et al. 2008) and partial or limited fasciectomy (Luck 1959; Hamlin 1952) or with the injection of collagenase (Hurst et al. 2009). Nevertheless, still some cases of severe progressive stage or severe recurrence are seen in specialized hand surgery centres (Moschella 2012). The treatment performed in order to extend and restore contracted fingers, in one or both hands, is usually aiming at lengthening of the skin, extending the retracted joints and re-establishing the flexo-extension functionality of the fingers and the physiological prehension of the hand. But even for an experienced surgeon, it is difficult to select the right surgical treatment for functional recovery. This has inspired us to propose a physiological lengthening of contracted fibrous structures of the fingers and of the hand by means of the Continuous Extension Technique (Messina 1989; Fig. 42.1).

Many fibrous structures are involved in the progressive contracture due to the disease (Millesi 1986): collateral ligaments; checkreins, volar plate; flexor tendon sheaths together with the pretendinous band, lateral cord, natatory ligaments, spiral cords and collateral neurovascular bundles; and at last the dermal fibrous structures together with a real alteration of sensitivity and trophism of collateral nerve endings. Additionally, having to re-establish useful sliding of different thick, fibrotic and contracted layers of soft tissues, many surgical procedures utilized until today create new and worse biological damage and scarring as in fact happens after the total anterior teno-arthrolysis (TATA Operation) (Saffar 1983) or radical and total fasciectomy (McIndoe and Bear 1958; Skoog 1948) or a large

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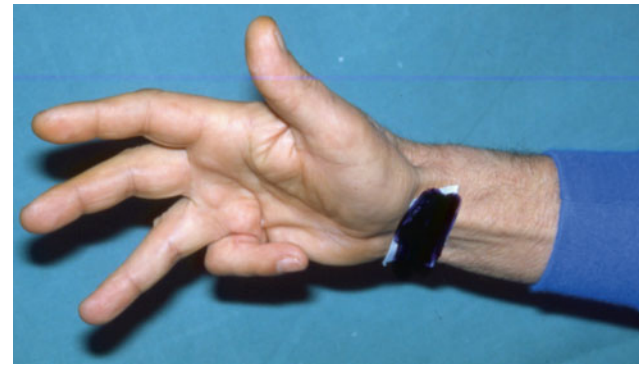

Fig. 42.1 Severe Dupuytren contracture of the little finger. This situation is presenting a difficult surgical approach; ankylosis of MP and IPP joints; contracture with important loss of digito-palmar and palmar skin (2–3 cm) and of digito-palmar fascia; severe retraction of collateral ligaments, checkreins and palmar plate of IPP joint; even the lateral and spiral cords are retracted as well as the natatory ligament. Due to complexity of reconstructive surgery, we suggested to utilize the Continuous Extension Technique

dermofasciectomy (Hueston 1984). Today, in the presence of a progressive disease, there is a worsening post-operation healing of sliding tissues of fingers together with poor functionality even of the hand; surgeons suggest performing a secondary or tertiary surgery; this choice additionally worsens all soft finger tissues and may ultimately lead to the indication of partial or total amputation of the finger. On the other hand, it is known that even in some severe cases, loss of vascularity of the contracted finger or alteration of its sensibility and trophism often leads to the indication of amputation. The Continuous Extension Technique can be used in cases of severe progressive Dupuytren Disease; avoiding and may help avoid an amputation.

42.1.1 Advantages and Indications of the TEC Methodology

The Continuous Extension Technique (TEC) is a minimally traumatic, painless and advanced technique performed by an external device which allows the restoration of the extension of the fingers and their function.

The Continuous Extension Technique:

1. Provides the option of conserving severely contracted fingers and restoring their functionality; this had previously strained the technical limits of classical operations or been downright impossible (progressive cases with persistent recurrences) (Messina 2011).
2. Facilitates all procedures, greatly reducing surgical tissue trauma, the complexity, length and difficulties of the surgery in long-term retracted joint stiffness.
3. Simplifies the finger and palmar skin incision and surgical approach; it avoids complementary articular procedures in the finger, such as capsulotomy and arthrolysis; the release of checkreins, collateral ligaments and palmar plate; and the release of the digital cord and the retracted lateral, spiral and natatory ligaments. This especially in advanced stage or in patients who have already been operated on.
4. Avoids the sudden surgical extension of the contracted finger with consequent stretching and tearing of collateral neurovascular bundles which cause devascularization and trophic trouble in fingers that have been retracted for many years in severe flexion due to progressive disease and recurrences (Fig. 42.2).
5. It is an alternative to dermofasciectomy and difficult plastic surgery for correcting severe digital or palmar skin loss and contracture.
6. Surpasses the McCash "open palm" technique both in theory and in its practical applications (no exposure of deep and sensible palmar tissues, no secondary healing, no deep scarring risk, no risk of flogosis, no risk of palmar reflex dystrophy, etc.).
7. TEC is a possible definitive solution in some cases of chronic Dupuytren contracture; this is confirmed by the disappearance of the pretendinous cord in the extended finger and of the contracted palmar fascia as well as the palmar

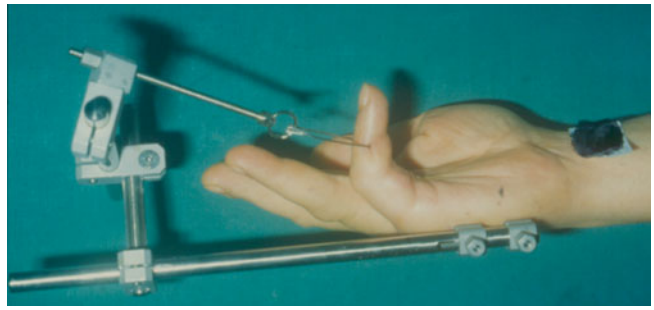

Fig. 42.2 The TEC device. The TEC device is an advanced apparatus to perform continuous extension treatment of the retracted fingers. The device is not cumbersome (its size can be adapted to the elongated fingers and it weighs only 190 g). The extension is minimally traumatic and painless; it can be applied simultaneously to several retracted fingers. The TEC avoids the sudden surgical extension of the contracted finger with consequent stretching and tearing of collateral neurovascular bundles which may cause disturbance of blood circulation and trophic trouble in fingers that have been retracted for many years in severe flexion due to progressive disease and recurrences

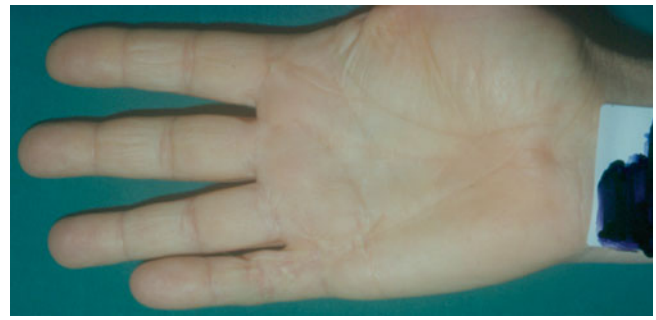

Fig. 42.3 Complete extension of the little and ring fingers (also partially contracted) after 3 weeks. The elongation is carried out by the patient at home. The fasciectomy of diseased fascia must be performed at the same time the TEC device is removed. The surgical approach is as simple as in the first stage of Dupuytren Disease. Plastic skin surgery, including Z-plasties, skin graft, etc., was not necessary in this case and in other cases treated by TEC methodology

nodules (compression test) (Fig. 42.3; Messina and Messina 1997).

8. TEC treatment might also benefit post-traumatic retraction scars accompanying flexion ankylosis and deformity of the fingers (caused by burns, tendon and osteoarticular trauma, skin loss, etc.).
9. Finally, TEC is indicated in severe progressive recurrences and extensions of advanced Dupuytren, reducing stages III and IV to the first stage of beginning of contracture (Messina 2011).

Repeated surgery can potentially lead to amputation of the recontracted finger, and the TEC device reduces this risk. For severe pathological contracture, the Continuous Extension Technique methodology is indicated to ease surgery and reduce complications. By lengthening of the digito-palmar fascia and of the contracted skin as well as of all retracted soft tissues, it re-establishes the first stage of the disease (Fig. 42.3).

42.2 Materials and Methods

We treated 130 patients from 2004 to 2014; they were affected by stages III and IV of Dupuytren contracture according to the Tubiana classification (Tubiana 1996). Of the 86 patients reviewed, the TEC procedure was applied to 21 previously not operated hands and 65 hands that showed recurrence or extension after a previous operation performed in another hospital. One third of cases (28 patients) had been indicated as needing amputation: 9 cases as first indication, 7 as a consequence of progressive recurrence and worsening after total fasciectomy, 5 after dermofasciectomy, 6 after secondary articular surgery and 1 after tertiary procedure.

42.2.1 Technique

Under regional or axillary block anaesthesia, two self-drilling pins with continuous threads are inserted on the cubital side of the hand through the skin. The pins are inserted transversally through the fifth and the fourth metacarpal bones at the proximal and distal metaphyses (Fig. 42.2).

Clinical and radiographic control of the length and position of the inserted pins confirms that they have completely penetrated both cortices of the fifth and fourth metacarpal bones. In this way we obtain a very stable and painless assembly that supports the TEC device in order to achieve a physiological, continuous elongation of the retracted fingers (Messina 1989; Messina and Messina 1991, 1993, 1995, 1997; Fig. 42.2).

A Kirschner wire is then inserted transversally through the distal metaphysis of P2, through the proximal metaphysis of P3 if this is retracted or through both metaphyses if both the proximal and the distal interphalangeal joints are flexed together in severe contracture (Fig. 42.2). The Kirschner wire is bent to form a traction loop. The TEC device is assembled on the metacarpal pins outside the operating room. The phalangeal traction loop is connected to a threaded screw allowing a 2 mm. per day lengthening of the retracted finger (2 mm. distributed four times a day: 8 am, 12 pm, 4 pm, 8 pm). The device is regulated with regard to adequate direction and height according to the respective extent of flexion and direction until complete elongation of the retracted finger has been achieved (Fig. 42.3). After its positioning the extension is performed by the patient himself for 3 weeks.

Then the pins, the Kirschner wire (s) and the TEC device are removed, and a partial palmar fasciectomy can be performed through a simple palmar surgical approach as the finger is completely extended so that even a less experienced hand surgeon can perform it. The hand and the finger(s) are then immobilized until stitches are removed. Afterwards a rehabilitation session begins together with paraffin baths and TENS sessions (TENS = Transcutaneous Electronic Nerve Stimulation). In the beginning it is better to reduce the functional stress of the finger(s) and the palmar skin to avoid forced and stretching rehabilitation of the operated finger and to carefully massage the palmar-digital skin.

42.3 Results

Around 86 hands and 119 fingers were reviewed with a mean follow-up of 4 years (8 months to 10 years).

1. Excellent and good functional results were obtained in 85 % of cases (Figs. 42.3 and 42.4).
2. Fair in 15 % (without perceptible improvement).
3. No poor result.
4. Stiffness 16 %.
5. Recurrence was observed in 8 patients with appearance of a nodule and small scar retraction on the previous incision line without deep

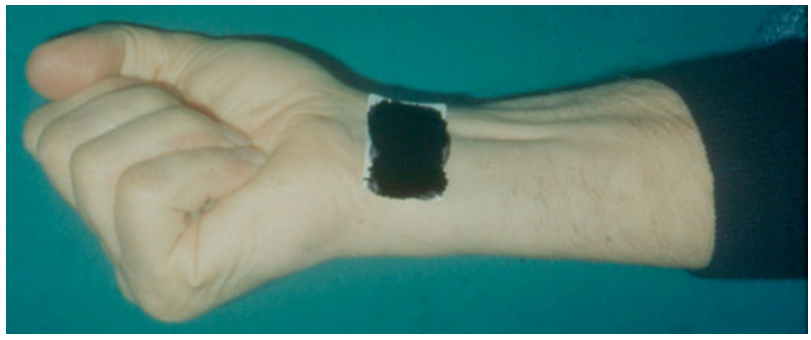

Fig. 42.4 Hand function after TEC. Active flexion of the fingers after application of the Continuous Extension Technique. Now joints are completely mobile without residual thickness and retraction of collateral and checkrein ligaments; volar plate and all fibrous structures of the contracted finger are physiologically lengthened and their elasticity restored

fibrosis; in 10 cases extension of disease appeared on the border of the operated area, with little nodules or light cords on the radial side of the hand.
6. No pain or painful scars were noted and skin sensitivity was found to be normal (comparable to the surrounding normal skin).
7. No flogosis, no algodystrophy was observed.

For 180 years Dupuytren Disease was considered a degenerative, progressive and irreversible disease. The Continuous Extension Technique may modify this view because the degenerative fascia can become regenerated by continuous lengthening; progression can be stopped by the external traction, and the irreversibility of the disease can be reversed and the progression stopped by means of our mechanical action.

The TEC methodology, by bringing the contracture back to the initial stage of the disease, has shown that the contraction process can be stopped and reversed.

The Continuous Extension Technique opens the way for new basic research into the morphological and biochemical processes of collagen in the retracted palmar fascia (Bailey et al. 1994; Brandes et al. 1994). Research by the laboratories of cell biology and electron microscopy of the Medical School of Hannover (Brandes et al. 1996) has revealed the unexpected appearance of "stress fibres" in the endothelial cells of both arterioles and venules in the contracted fascia of Dupuytren Disease after application of a TEC device. These fibres have never been seen before in these structures. This confirms the scientific importance of the TEC method in studies of Dupuytren Disease and its clinical originality. It could explain the morphological basis of the mechanism of the contracture of the fascia in Dupuytren Disease and its recurrence.

42.4 Discussion and Conclusion

The Continuous Extension Technique (TEC) represents an alternative to finger amputation in severe cases of Dupuytren Disease. It is a means for avoiding necrosis, loss of vascularity and functional impairment that may result from classical operations. At the end of the continuous extension, a considerable improvement in elasticity, skin trophism and microvascularity of the extended skin was always observed. This technique is an advanced method and achieves the elongation of contracted skin and of the digitopalmar fascia in severe and inveterate Dupuytren Disease (Figs. 42.3 and 42.4); it enables the retracted fibrous tissues to revert to the first Tubiana stage of the disease. TEC is a minimally traumatic and painless method for the rational treatment of some cases where there is interdigital mycotic intertrigo, together with a severe or progressive disease of one or several digits. It avoids the sudden surgical extension of the retracted finger and the stretching of collateral vasculo-nervous bundles which are the cause of devascularization and trophic difficulties in fingers retracted for many years in complete flexion. The resulting elongation of the retracted skin and the contracted fascia goes up to 3 cm (Messina and Messina 1997), thus avoiding plastic skin surgery and complementary articular procedures.

The treatment is indicated as an alternative to a proposed finger amputation or if a multiple operation plan is needed. A fasciectomy after TEC procedure is as simple as in stage I of Dupuytren Disease.

Conflict of Interest Declaration The authors have no conflict of interest to declare.

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Experience in Treating Patients with Stage IV of Dupuytren Contracture (PNF vs. Fasciectomy)

43

Andrei Zhigalo, Alexander Silaev, Victor Morozov, and Vitaliy Chernov

Contents

43.1 Introduction

Treating patients with stage IV of Dupuytren contracture is a complicated and challenging task of modern hand surgery. This is due to the high risk of complications after surgery (altogether about 76 %) and a high level of unsatisfactory results of up to more than 40 % (Dias and Braybrooke 2006; Denkler 2010; Shih and Bayat 2010; Desai and Hentz 2011).

43.2 Goal of Study

Improving results of treating patients with Dupuytren contracture stage IV by creating a decision flowchart to help choose the optimal treatment option based on the clinical situation.

43.3 Materials and Methods

We have studied results of treating 214 patients with stage IV of Dupuytren contracture as defined by R. Tubiana's classification. Patients were divided randomly into two groups, one for treatment with needle fasciotomy and one for limited fasciectomy. The two groups were similar in terms of cords in the palmar aponeurosis, contractures, affected joints, and some other factors, e.g. skin retractions and their size, existence of Dupuytren nodules, and quality of the skin in

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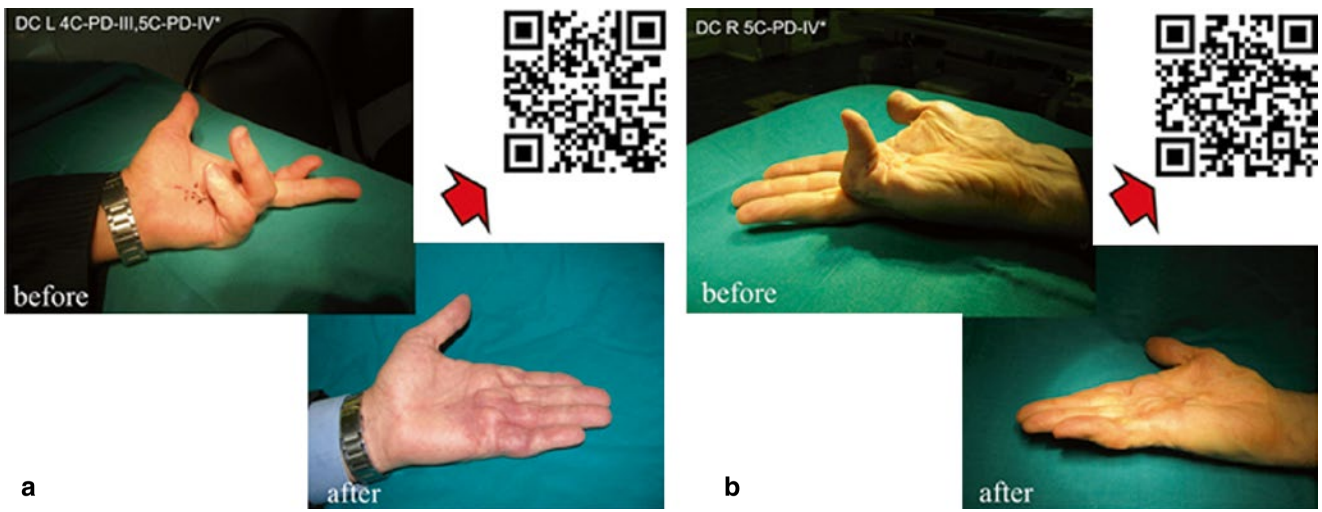


Fig. 43.1 Results of PNF in patients with stage IV of Dupuytren contracture (group 1). (**a**) Left hand of a 72-year-old patient with Dupuytren contracture before and 21 days after needle aponeurotomy and rehabilitation treatment, (**b**) Right hand of a 64-year-old patient before and after needle aponeurotomy and rehabilitation treatment. QR codes for videos demonstrating hand function before and after the operation

general. The two teams of surgeons were headed by the same surgeon; the skills level of surgeons within these two groups was equal, and we presume that different skills could not significantly affect our results.

43.3.1 Percutaneous Needle Fasciotomy

Patients in group 1 (127 patients) received percutaneous needle fasciotomy (PNF) under outpatient conditions (Fig. 43.1). We achieved corrections of single finger joints by 90–100°. In the postoperative period, correction of the residual contracture was accomplished with the help of an individual orthosis made of thermoplastic and increasing the extension daily by to 5–10°. Additionally physiotherapy was applied using phonophoresis to support a topically applied complex of collagenase for treating scarring (brand name Fermencol). Night splinting holding the hand in the maximum extension position was maintained until 10 weeks after PNF. 56 patients with nodules in the palmar aponeurosis were additionally injected with steroids at the time of the aponeurotomy. Full functional recovery was achieved on days 14–21.

In 21 patients with early recurrence (within 6 months), a limited resection of the aponeurosis was performed as a second stage of treatment.

43.3.2 Limited Fasciectomy

All patients in group 2 (86 patients) received limited fasciectomy (LF) using microsurgical techniques. In the postoperative period, all patients received rehabilitation therapy. Primary correction of flexion contracture did not exceed 100°. After fixating the finger with the K-wire, we were able to get 140–150° correction. Fixation was used for PIP joints only and for 2–4 weeks. Wounds were closed primarily with the use of different methods of skin plastics using local tissues. Time in hospital was 4–7 days. Function was recovered within 4–20 weeks (Fig. 43.2).

43.4 Results

Treatment results were rated using the qDASH system. The observation period was typically 2 years (maximum of 6 years) after operation. In all cases

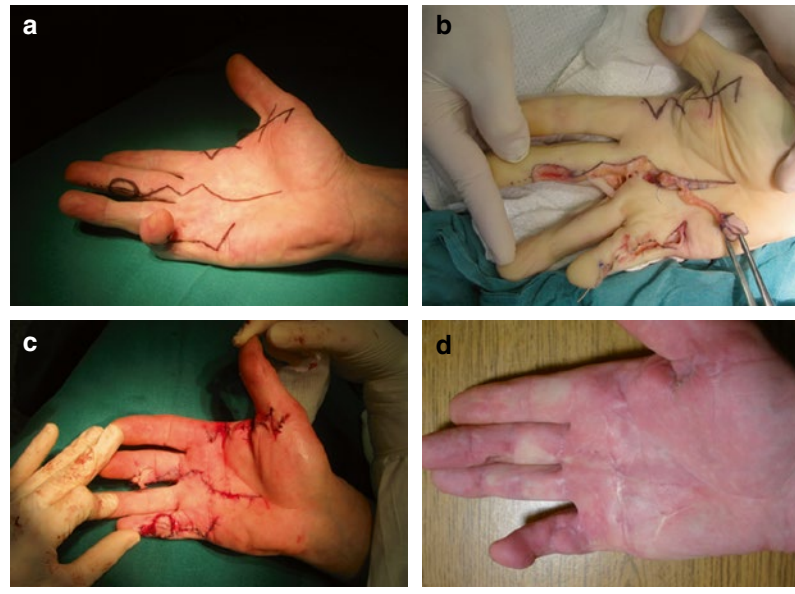
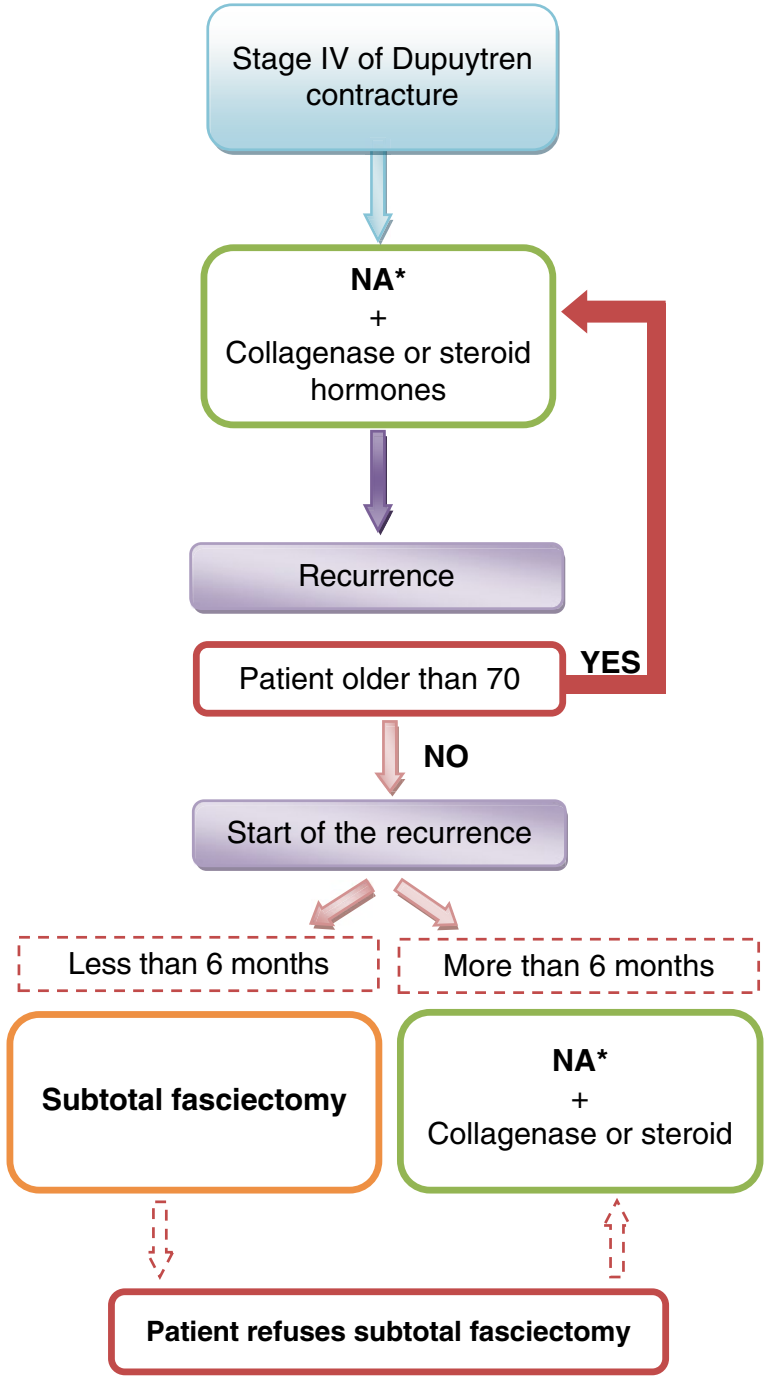


Fig. 43.2 A 51-year-old patient with LF of stage IV of Dupuytren contracture and relapse (group 2). (**a**) Before operation; (**b**) palmar aponeurosis removed and skin-fascial pedicle flap from the middle finger is elevated; (**c**) end of the operation, wounds are closed; donor defect is covered with full-thickness skin graft from the anterior aspect of the elbow region (Wolfe's graft); (**d**) recurrence at the same hand 3 months after the operation. The skin graft was used when it was impossible to close a defect using Z-plasty (9% of cases)

Flowchart for choosing the procedure of treating patients with stage IV of Dupuytren contracture



* NA = Needle Aponeurotomy = PNF

of both groups, full correction of flexion contracture in MCP joints was achieved, but in PIP joints residual joint contractures up to 1–9° in group 1 and 10–20° in group 2 were often present.

Complications in group 1 were ruptures and deep skin splits (9 %), in group 2 skin edge necrosis (28 %), neurodystrophic syndrome (15 %), and infection (2 %). Suppurative complications occurred in 3.9 % of group 1 and 5.6 % of group 2. One patient (0.25 %) from group 1 had iatrogenic damage of the flexor tendon. Excellent results were observed in 56.4 % (group 1) and 18 % (group 2), good in 28.1 (group 1) and 15 % (group 2), satisfactory in 10.4 % (group 1) and 40 % (group 2), and unsatisfactory in 5.1 % (group 1) and 27 % (group 2). Recurrence was observed in 42 % (group 1) and 7.5 % (group 2).

Conclusions

For patients with stage IV of Dupuytren contracture, PNF in combination with topical collagenase in the posttreatment period gives better results and less complications than limited fasciectomy. Patients with quickly developing recurrence can be considered for a subtotal fasciectomy as a second stage of treatment. Using this two-step approach gives better results than just aponeurotomy for patients with stage IV of Dupuytren contracture.

Conflict of Interest Declaration None to declare.

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Controversy: Splinting for Dupuytren Contracture

44

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44.1 Introduction

Ilse Degreef

The application of a splint as a conservative treatment may have a beneficial effect in Dupuytren contracture, but as a postoperative intervention, it has become routine despite a lack of evidence. By resisting the contracture, it should help extend the finger and may help patients feel they can control their disease for which there is no cure. However, recent randomised studies of postoperative night splinting in addition to hand therapy have shown no significant benefit and possibly even a worse result. Thus, the application of a splint in Dupuytren Disease remains controversial, and we present opposite views to allow better understanding of the debate.

First, Adrian Chojnowski will defend the position that splinting confers no benefit, followed by Wolfgang Wach defending that splinting can be beneficial. The conclusion is a joint effort of both authors attempting to merge their views.

44.2 Splinting Confers No Benefit

Adrian Chojnowski

44.2.1 Introduction

As much as the patient, surgeon and therapist would like to believe that the adjunct of a splint

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postoperatively or used as a nonoperative intervention can improve a Dupuytren contracture, there is little evidence to support this notion. Studies of splinting as a nonoperative treatment involve small series of patients who receive other treatments such as friction massage and passive stretch. Postoperatively there is better evidence from two larger studies that the routine addition of a night splint confers no overall benefit. A third specifically targeting PIP joint contracture showed no difference but a trend for a better result with no splint. So a splint may not only confer little or no benefit, it might actually make things worse whilst it inconveniences the patient.

44.2.2 What Is a Splint?

Splints used in Dupuytren Disease are usually hand based applied to the dorsum or palmar aspect and apply a tension force along the digit to achieve an extension gain. They are made from thermoplastic material that can be moulded to the desired shape when warm, maintaining shape as they cool (Figs. 44.1 and 44.2). Apart from the variation in manufacture quality which can have significant influence on patient compliance (if it is uncomfortable or falls to bits then it won't be used), how tension is set needs to be considered. Evans et al. (2002) proposed the "no tension" principle when a splint is used postoperatively. For the first few postoperative weeks, the splint was applied to the hand without tension across the wound. After this, the digit(s) was placed to achieve comfortable extension. Many therapists use this principle as they believe excessive early tension causes a scar flare response with excessive oedema, pain and stiffness. A more aggressive therapy regime may include "maximum" extension setting using the splint to achieve the highest tension that can be tolerated. In summary, there are many variables in how a splint is used as a treatment tool for Dupuytren Disease.

Fig. 44.1 A dorsal hand-based thermoplastic splint

Fig. 44.2 A volar hand-based thermoplastic splint

44.2.3 The Role of Postoperative Splinting

Some surgeons routinely advise postoperative splinting after fasciectomy and dermofasciectomy. This has also filtered down to some patients post percutaneous needle fasciotomy (PNF). The training brochure for collagenase *Clostridium histolyticum* injections (Pfizer publication 2011) recommends night splinting for up to 4 months as this was used in the clinical development programme. However, three randomised trials indicate that extension splinting is not necessary after surgery.

Jerosch-Herold et al. (2011) conducted a pragmatic, randomised, multicentre trial of 154 patients undergoing fasciectomy or dermofasciectomy in the UK. Randomisation took place after surgery with 77 patients receiving normal hand therapy and 77 receiving hand therapy plus a volar hand-based thermoplastic night splint to be worn for 6 months and complete a splint diary. Tension was set using the Evans "no tension" principle. Ethically, as it was unknown if a splint might be useful, if a finger recontracted by 15° at the PIP and 20° at the MCP joint beyond the first postoperative measurement, a night splint could be applied. 13 of 77 patients in the non-splinting group recontracted beyond these parameters and subsequently received a splint. There was no difference between the groups at 3, 6 and 12 months in satisfaction, active flexion/extension and the DASH score (Disability of the Arm, Shoulder and Hand) on an intention to treat analysis. 84 % of the splint group and 77 % of the crossover patients used the splint for 50 % or more of the nights. The conclusion is that the routine use of a night splint conferred no benefit but could be used if a contracture starts to recur.

Collis et al. (2013) used similar methodology in NZ with 26 patients receiving therapy and a dorsal hand-based night extension splint and 30 patients receiving hand therapy alone after fasciectomy. 3 patients in the splint group received a splint due to recontracture. At 3 months follow-up, there was no difference in DASH scores, total active extension and flexion between groups.

Kemler et al. (2012) randomised patients to hand therapy with a splint or therapy alone. The inclusion criteria targeted a Dupuytren Disease subtype that is generally thought of as more difficult to successfully treat – PIP joint contracture of greater than 30° undergoing fasciectomy. The study protocol did not allow for crossover if recontracture occurred; the splint was dorsal hand or forearm based and worn full time for 4 weeks and then night only for 2 months. One year after surgery, the splint group had a mean reduction of 21° in PIPJ flexion contracture and the hand therapy alone group 29° (a better result but not statistically different).

There seems little benefit to the routine addition of a night splint to normal hand therapy practice.

44.2.4 Splinting as a Nonoperative Treatment

Laboratory-based studies which grow Dupuytren fibroblasts in a collagen matrix show increased contraction in response to a tensile load (Bisson et al. 2004). Such applied forces are short-lived (over hours/few days), and there is no evidence that such a model can translate to practical splinting tips although it does raise some interesting questions. Two small studies have investigated the use of a splint as a nonoperative treatment. Ball and Nanchahal (2002) looked at 6 patients using a volar-based night splint with 6–24 months follow-up. Only 2 patients were able to comply with a splint regime over 2 years but did show improvement of their MCPJ contractures (12 to 0 and 30 to 22°).

Larocerie-Salgado and Davidson (2011) asked 13 patients (19 digits) to wear a volar hand-based thermoplastic splint at night and perform passive stretch/friction massage. One patient left the study and underwent surgery. PIPJ extension in the remaining 12 patients improved on average by 14.6° (pre-splint range 15–60°) at mean follow-up of 12.6 months in 13 of 19 digits. 2 digits showed no difference and were deemed to have stabilised. The average age was 69.4 years. The

later effect on the Dupuytren contracture if splinting were to cease is unknown.

Acknowledgement and Conflict of Interest Declaration The author is grateful for the help of Debbie Larson for hand therapy advice and manuscript review. The author was the local principal investigator for the POINT X open-label 3B collagenase trial. He received payment into his research account from Pfizer for recruitment of 10 patients as per protocol. The account is administered by the Norfolk and Norwich University Hospital NHS Trust.

44.3 Splinting Is Beneficial

Wolfgang Wach

44.3.1 Introduction

Wearing a night splint for some period of time is frequently suggested after treating Dupuytren contracture with PNF (percutaneous needle fasciotomy), collagenase injection or surgery. Clear and undisputable evidence of the efficiency of these recommendations is still missing. Nevertheless there is some evidence encouraging further investigations and using splints. This chapter is addressing the use of static night splints for longer-term night splinting (months or years), not short-time splinting (days), immediately after treatment (Clare et al 2004).

44.3.2 Anecdotal Evidence

Anecdotal evidence can be found, for example, in the forum of the International Dupuytren Society (IDS 2015) and in reports from members of the IDS. Here are a few examples:

The patient Stefan H, having had 8 surgeries and 1 PNF, reports that night splinting was required after surgery of recurrence or when the contracture had persisted over a longer period of time (years). Also after PNF he considers night splinting a necessity to avoid quick recurrence.

Barry N had 15 surgeries, including 4 dermofasciectomies, and 3 PNFs. He reports that he needed no splinting after surgery, provided the finger became straight, but found splinting after PNF beneficial to avoid or postpone recurrence.

Rainer Z had 2 PNFs. He wore a night splint for 3 months and now wears it for a week whenever he feels that a finger starts contracting. So far he has succeeded in maintaining his PNF results over 8 and 3 years, respectively.

John C had 2 PNFs. After the first PNF, he wore no night splint and after the next PNF, which was carried out by another doctor, he reports: "She prescribed an additional procedure, that being keeping a splint on my hand for 90 days while I slept. That has helped immeasurably".

The patient OJ had 1 PNF. He wore a night splint for 3 years and maintained the PNF result. He then lost his splint when moving and didn't care getting a new one. He experienced recurrence to the initial state within a year.

The author himself had partial fasciectomy (20 deg MCP of the ring finger) 15 years ago and did not wear a splint after surgery. The postoperative treatment was simple bandaging until the wound had healed and some physiotherapy. After 15 years his hand is still fully functional and shows no signs of recurrence. But he also had collagenase injection (45 deg PIP of the little finger). The extension deficit was not completely eliminated, about 20 deg remained. He was able to maintain this result for 14 months whilst wearing a night splint regularly. He then stopped splinting because he felt that the splinted hand eventually became stiffer, not only in the morning but also during the day. He had recurrence to the original amount of contracture within 4 months.

44.3.3 Case Studies

Reports from patients are sometimes unclear, are typically lacking documentation and leave many questions open. Better documented are case

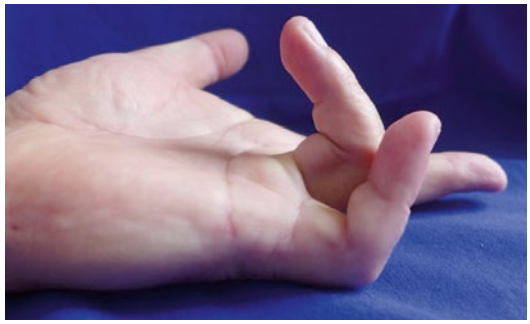

Fig. 44.3 Patient prior to treatment

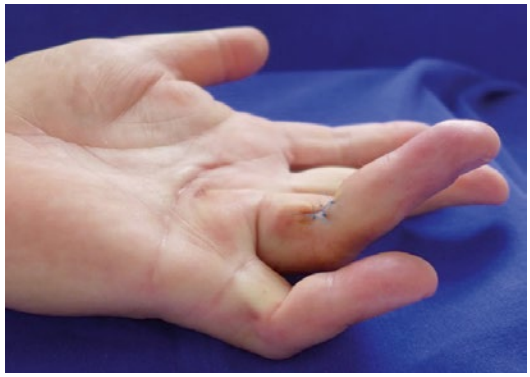

Fig. 44.4 Result of PNF, immediately after treatment

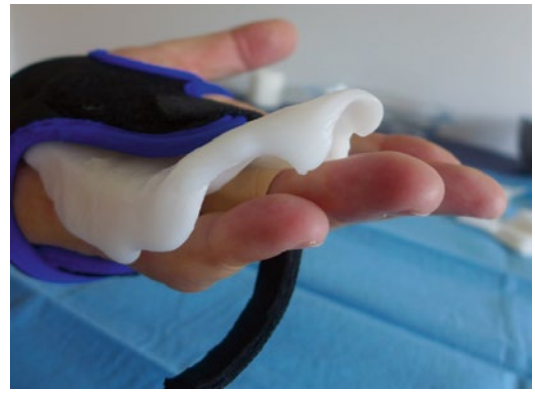

Fig. 44.5 After 1 week

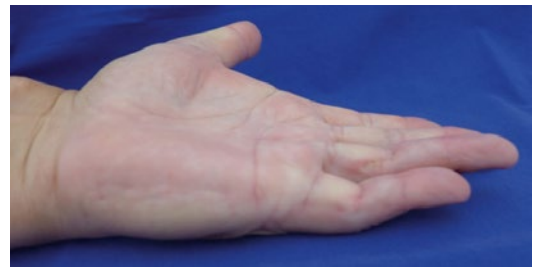

Fig. 44.6 After 2.5 months of splinting

studies. Here is an example, provided by Albrecht Meinel, from Germany. The patient is a 58-year-old man with Tubiana stage II/III contractures in the left hand (Fig. 44.3).

The usual recommendation for this stage of disease would probably be surgery. Yet the patient did not want to undergo surgery and decided for PNF. Figure 44.4 shows the results immediately after PNF.

The patient then regularly wore a night splint. Within the next weeks, his hand opened further (Fig. 44.5), and the result was maintained and even slightly improved over the months whilst continuing to wear a night splint (Fig. 44.6). The patient is completely happy with the result.

Further cases demonstrating positive short- and long-term effects of passive night splinting are reported e.g. by A Meinel (2011, 2012, 2014).

44.3.4 Studies Indicating Positive Effects of Splinting

Rives et al. (1992) investigated the use of dynamic splinting after fasciectomy of severe PIP joint contractures. 6 months of dynamic extension splinting was applied on 20 patients, who had 23 PIP joints operated (contractures 45–110 deg). Initially a splint was also worn during the day. Thirteen patients (14 digits) complied with the program, wearing the splint at least 50 % of the recommended time. Seven "non-compliant" patients (9 digits) did not wear the splints half the time. "In the compliant group, mean improvement was 59 %. Eleven of 14 digits maintained an average of 75 % improvement in proximal interphalangeal joint extension at 2 years". The results of the non-compliant group were far poorer: 25 % "improvement in proximal interphalangeal joint extension over preoperative values was noted at 2 years".

Degreef and Brauns (2016) report positive results of splinting in their medical center, specifically with compression splinting: "an intense splinting regimen significantly reduced the flexion contracture with a mean of over 45° in compression splinting".

Ball and Nanchahal (2002) researched the preventive effect of splinting *without prior treatment*. "The purpose was to assess if static splinting could control the flexion deformity and if MCP and PIP joint extension could be increased". 6 patients participated in this small study (3 PIPs, 4 MCP joints). At 4 months the attending patients (5 out of 6) showed improvements between 4 and 60°. Two patients then stopped splinting and for both of them, the contracture returned within 2 months, about 10° worse than initially. Two patients (3 MCP joints) continued splinting for 2 years but in an on/off mode, wearing the splint 3–4 nights per week. At 24 months they were still showing less contracture than initially, one of them exhibiting no contracture anymore.

44.3.5 Discussion

Anecdotal evidence is considered not very reliable and the lowest level of evidence (Burns et al. 2011). Anecdotal evidence is certainly not sufficient when, for example, pharmaceutical research is considered, where sometimes severe side effects have to be weighed against a potential benefit. Burns et al. suggest for the lowest level of evidence, "Clinicians should consider all options in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm". Splinting after treating Dupuytren contracture is essentially harmless (Kemler et al. 2012; Rivlin et al. 2014). If there is anecdotal evidence that splinting might be beneficial, it is encouraging to try it, even if based on the lowest level of evidence.

Evaluating the effect of splinting in a trial is difficult for several reasons. The effect may well depend on the specific joint, the previous amount of contracture, the time period for which the splint was worn, the type of splint and last, certainly not the least, the compliance of the patient. Furthermore, the available studies referenced above are so low powered that they are coming close to a summary of case studies, and they are addressing situations that are not typical. Nighttime splinting typically uses passive (static) splints and is only applied after treatment. For the time being, the evidence of the benefit of splinting is on the level of observed cases and anecdotal reports.

A trial concluding that splinting confers no benefit (Jerosch-Herold et al. 2011) had a higher number of participants (154), was randomised and multicentric but is still suffering from problems like using different splints and having little control of the critical patient compliance ("verification of actual splint wear was not possible"). Interesting enough the authors of this study themselves recommend splinting in case of recurrence and report for their non-splinting group: "if the patient had a net loss of 15° or more at the PIPJ and/or a net loss of 20° or more at the MCPJ of the operated fingers, they were then given a splint and splint diary". A later study by Kemler et al. (2012) randomised patients after PIP surgery and did not allow any splinting in the non-splinting group. It did not find any evidence for a benefit of splinting but is suffering from the fact that night splinting was stopped 3 months after surgery, and results were measured 12 months after surgery, i.e. after 9 months of no splinting.

Acknowledgement and Conflict of Interest Declaration
The author is grateful to all patients sharing their experience with splinting and to Albrecht Meinel, Dupuytren-Ambulanz, Germany, for providing pictures and advice. The author has no competing interests.

Conclusions

The question whether splinting is beneficial or not is still open and further trials are required. There is no evidence that the routine addition of a night splint to postoperative hand therapy offers a significant advantage to the patient. There is some evidence that prolonged splinting in addition to hand therapy may control Dupuytren contracture as a nonoperative

treatment, specifically in a more elderly group. From case reports describing positive effects of splinting and studies exhibiting no benefit after surgery, a pattern can be concluded, which is summarised below:

- Splinting can be used as a nonsurgical treatment. Prevention may work for only as long as the splint is worn.
- Routine night splinting is not required in addition to hand therapy after primary surgery.
- Early recontracture after surgery might be due to scar contracture, and compression therapy needs to be researched further.
- A splint might be beneficial for:
  - Revision surgery or capsular joint contracture
  - Minimally invasive techniques, specifically for patients subject to early recurrence
- There seems to be no time period after which the result can be expected to be stable. When splinting is stopped, the contracture may return within months. This needs to be considered when designing future trials.

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Xiapex Injection Training Brochure (Pfizer March 2011)

Part IX

Related Diseases and Other Treatments

Marie Badalamente and
Heinrich Seegenschmiedt,
supported by David O'Gorman

Introduction to Radiation Biology When Treating Hyperproliferative Benign Diseases

45

Franz Rödel and M. Heinrich Seegenschmiedt

Contents

45.1 Introduction

While the application of radiation therapy to treat hyperproliferative benign diseases is still controversial and incompletely known by non-radiation physicians, long-term clinical experiences and studies clearly indicated a patient's benefit (Seegenschmiedt et al. 2008; Seegenschmiedt et al. 2015). Accordingly, radiation therapy with low doses has been successfully implemented in the treatment schedules of a variety of such disorders including heterotopic ossifications, prophylaxis of keloid relapse after surgical excision (Suit and Spiro 1999), avoidance of relapse after resection of pterygium (Smitt and Donaldson 1999) and diseases like palmar and plantar fibromatoses (Seegenschmiedt et al. 2008). The radiobiological basis and molecular/cellular mechanisms contributing to the modulation of these benign hyperproliferative fibromatous disorders, however, are far from being fully explored. This chapter thus aims to summarize current concepts of the antiproliferative and immune-modulating properties of a low-dose radiation therapy.

45.2 Basis of Hyperproliferative Diseases and Factors Involved

Aberrant cell proliferation is involved in the formation of hyperproliferative tissue formation, which is induced by either a genuine unknown

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reason, by secondary injury or by a variety of trigger mechanisms (Cordova et al. 2005). DD and LD are characterized by proliferation of fibrous tissue to form nodules and cords that have features in common with benign neoplastic fibromatosis (Rodemann and Bamberg 1995; Grenfell and Borg 2014). In general, the course of these diseases comprises three consecutive phases, which are associated with different radiation responsiveness:

1. A radiosensitive hyperproliferative initial phase characterized by increased numbers of fibroblasts/myofibroblast and early nodule and cord formation
2. The involutional phase with decreased radiation sensitivity in line with the establishment of fibre bundles resulting in contractures
3. A non-radiation-sensitive residual phase with collagen fibres dominating the connective tissue (Fitzgerald et al. 1999; Seegenschmiedt et al. 2008)

Consequently, the rationale for the use of ionizing radiation to affect these hyperproliferative disorders may be related to the presence of radiation-sensitive target cells like mitotic fibroblasts/myofibroblasts and molecular mechanisms. Molecular mechanisms include induction of free radicals to impair proliferative activity of these cells, interference with growth factors and cytokines and a reduction of activated immune cells involved in the inflammatory process and myofibroblast proliferation (Rubin et al. 1999; Yarnold and Brotons 2010). Mechanisms of modulating fibrogenic and inflammatory components by ionizing radiation are briefly described below.

45.2.1 Proliferating Mitotic Fibroblasts/Myofibroblasts Are Radiosensitive Cells

With regard to radiation-responsive target cells, the proliferative phase seems to be the most relevant, as it is mainly driven by radiation-sensitive fibroblasts and myofibroblasts prior to the formation of nodular contractures (Gabbiani et al. 1971; Rudolph and Vande Berg 1991). In response to fibrogenic cytokines released by inflammatory cells (e.g. macrophages) and other cell types, fibroblasts differentiate into myofibroblasts (Shih and Bayat 2010; Hinz et al. 2007). This process, referred to as activation, results in proliferation and excessive production and matrix deposition of extracellular components, most prominently collagen, fibronectin, elastin and proteoglycans and development of nodules and cords (Berndt et al. 1994; Abraham et al. 2007; Hinz et al. 2007; Dolmans et al. 2011). The cellular source of these myofibroblasts is not entirely clear; however, they may include resident or circulating stem cell-like progenitor cells like CD34, CD45, major histocompatibility complex II and collagen I-positive fibrocytes (Iqbal et al. 2014).

Concerning ionizing radiation, however, an alternative description of fibrocytes exists that differs from the one given above. In their analyses, Bayreuther and Rodemann defined fibrocytes as terminally differentiated senescent (postmitotic) cells with downregulation of c-fos and a specific capacity for the synthesis of collagen types I, III and V and proteoglycans (Bayreuther et al. 1988a; Bayreuther et al. 1988b; Rodemann and Bamberg 1995). Taking this definition into account, single-dose irradiation of fibroblasts in the dose range of 1–8 Gy induces terminal differentiation into senescent fibrocytes at a high percentage level, while irradiation of long-term cultures of fibroblasts with repeated doses of 10×0.6 Gy or 1.0 Gy revealed a marked reduction of fibroblast proliferative capacity (Rodemann et al. 1991; Bumann et al. 1995). Moreover, the life span of senescent fibrocytes is limited and shortened by approximately 40–45 % if induced by ionizing radiation as compared to physiological development (Bayreuther et al. 1992). Consequently, these populations have to be renewed from the mitotically active progenitor fibroblast pool (Herskind and Rodemann 2000), and thus disturbances in the differentiation processes in line with eliminating proliferating precursor fibroblasts may comprise a further basis for the clinical benefit of radiation therapy.

45.2.2 Free Radicals Impair Proliferative Activity of Fibroblasts

Following environmental stress including ionizing radiation, levels of reactive oxygen species (ROS) including superoxide (O_2-), hydrogen peroxide (H_2O_2) and hydroxyl radical (·OH) increase dramatically resulting in a significant damage to cellular macromolecules, induction of DNA damage and disturbance of a multitude of signal transduction pathways (Travis 2001; Richards et al. 2011; Nathan and Cunningham-Bussel 2013). The latter directly affect the production of inflammatory and fibrogenic cytokines that act as chemoattractants, mitogens and differentiation inducers for the fibroblast/myofibroblast/fibrocyte system (Robbins and Zhao 2004; Zhao and Robbins 2009). As such, a complex and multilevel expression network of pro- and anti-inflammatory cytokines, ROS and antioxidants exists within the tissue microenvironment after irradiation. An interrelationship between ROS production, localized ischemia and Dupuytren contracture has become evident from an early study (Murrell et al. 1987) showing six times elevated level of hypoxanthine and xanthine oxidase activity to catalyze elevated levels of O_2- and H_2O_2 in palmar fascias. Importantly, the addition of free oxygen radicals to cultured fibroblast from MD palmar fascia dose dependently either increases collagen type III expression (low concentration) or inhibits proliferation at higher concentrations (Murrell et al. 1990). Thus, elevated levels of ROS induced by ionizing radiation may exceed a threshold of ROS production to inhibit fibroblast/myofibroblast proliferation.

45.2.3 Cytokines and Growth Factors as Targets of Ionizing Radiation

Similar to wound healing and fibrosis, elevated levels of growth factors, cytokines produced by platelets, macrophages and other cell types have been reported in MD specimens. These factors include among others fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), connective tissue growth factor (CTGF), isotypes of transforming growth factor-β (TGF-β), interleukins (IL-1, IL-6), vascular endothelial growth factor (VEGF) and tumour necrosis factor-α (TNFα) (Alman et al. 1995; Badalamente et al. 1996; Cordova et al. 2005; Verjee et al. 2013; Bianchi et al. 2015).

Among these mediators, TGF-β1 and its downstream Smad signalling pathway is well recognized to constitute a key player (Kloen et al. 1995; Krause et al. 2011) and is undoubtedly one of the cytokines most relevantly involved in the process of fibrosis induction. TGF-β1 produced by a wide range of inflammatory, mesenchymal and epithelial cells converts fibroblasts into matrix-producing myofibroblasts and is critical in many facets of fibrogenic process, such as ROS generation and synthesis of extracellular matrix (ECM) compounds (Alioto et al. 1994; Badalamente et al. 1996). Notably, Wong et al. report on a negative-feedback inhibition of TGF-β1 at higher concentrations in Dupuytren fibroblasts. While lower concentrations (1–10 ng/ml) increase myofibroblast activation in an experimental collagen model, higher doses (20–30 ng/ml) inhibited contraction in Dupuytren fibroblasts (Wong and Mudera 2006). Consequently, increased TGF-β1 gene transcription and secretion triggered by ionizing radiation and mediated by transcription factors of the AP-1 and NF-κB family in endothelial cells and fibroblasts/fibrocytes (Rodemann et al. 1991; Bumann et al. 1995; Rödel et al. 2010) may result from elevated TGF-β1 levels capable to inhibit fibroblast/myofibroblast proliferation and ECM deposition in irradiated tissue.

45.2.4 Modulation of Macrophage Activity in Inflammatory Processes and Myofibroblast Proliferation

Although the onset and progression of DD and LD have extensively been investigated, the mechanistic basis for the proliferative elements is still

not completely resolved. However, the process includes at least two important components: a fibrogenic/angiogenic proliferative and an inflammatory or immune cell component. Indeed, histological studies identified the presence of immune cells in early Dupuytren contracture. In particular, the number of macrophages correlates with the quantity of myofibroblasts (Verjee et al. 2013; Andrew et al. 1991).

With regard to cytokine production, a hampered pro-inflammatory TNF-α and IL-1 secretion from human RAW 264.7 or murine macrophages stimulated by lipopolysaccharide (LPS) has been reported (Tsukimoto et al. 2009; Lodermann et al. 2012). Mechanistically, the hampered cytokine production was correlated to a diminished nuclear translocation of the immune relevant transcription factor NF-κB subunit RelA (p65) in line with a decreased expression of NF-κB upstream p38 mitogen-activated protein kinase (MAPK) and downstream factors like protein kinase B (Akt). Additionally, irradiated inflammatory macrophages exhibited a reduced oxidative burst capacity and diminished activity of inducible nitric oxide synthase (iNOS) upon a low-dose irradiation, resulting in reduced levels of ROS (oxidative burst) and nitric oxide (NO) production (Hildebrandt et al. 2003a; Schaue et al. 2002). Taking into consideration the prominent role of macrophages in both inflammatory and fibrinogenic processes, a diminished production of cytokines, ROS and NO may further contribute to a reduced myofibroblast proliferation/activation and to the beneficial effect of radiation therapy.

In line with that, Verjee et al. reported that targeting TNF-α diminished contractile activity of myofibroblasts indicating the factor to constitute a therapeutic target in Dupuytren Disease to downregulate the myofibroblast phenotype (Verjee et al. 2013).

It has further been suggested that a therapeutic benefit of steroids in early Dupuytren contracture may be due to diminished leukocyte recruitment (Meek et al. 1999) as well as increased apoptosis of macrophages and fibroblasts (Meek et al. 2002). In line with that, endothelial cells (ECs) are crucially involved in the regulation of inflammatory processes both by a local recruitment of immune cells from the peripheral blood (adhesion) and their capacity to secrete a multitude of cytokines/growth factors (Speyer and Ward 2011). Applying adhesion assays, we and others have reported on a reduction of leukocyte adhesion to 40–50 % of the control level at 4 and 24 h after a low-dose X-irradiation (Kern et al. 2000; Hildebrandt et al. 2003b; Rödel et al. 2002). Interestingly, this functional characteristic is mediated by the expression of TGF-β1 from the EC. Based on these investigations, it is reasonable to assume that a reduced recruitment of immune competent cells like monocytes/macrophages or granulocytes may further contribute to the antiproliferative and functional effects of radiation treatment in DD or LD.

Conclusion

As depicted in Fig. 45.1, hyperproliferative diseases may be based on complex (patho) physiological networks and considered to comprise systems biology diseases (Rehman et al. 2011). Accordingly, one may assume that the empirically proven beneficial efficacy of (low-dose) radiation therapy is mediated by the modulation of a multitude of cellular components and pathways involved. Although considerable progress has been achieved during the last decade in the understanding of radiobiological mechanisms being prominent at a low-dose radiation exposure (Rödel et al. 2012; Rödel et al. 2015), clinical effects may originate from an overlap of multiple pathways that are initiated at various thresholds, display different kinetics and operate in a staggered manner. Thus, intensive translational and clinical research efforts as well as the development of further basic preclinical models are seriously needed to unravel additional contributing factors and mechanisms.

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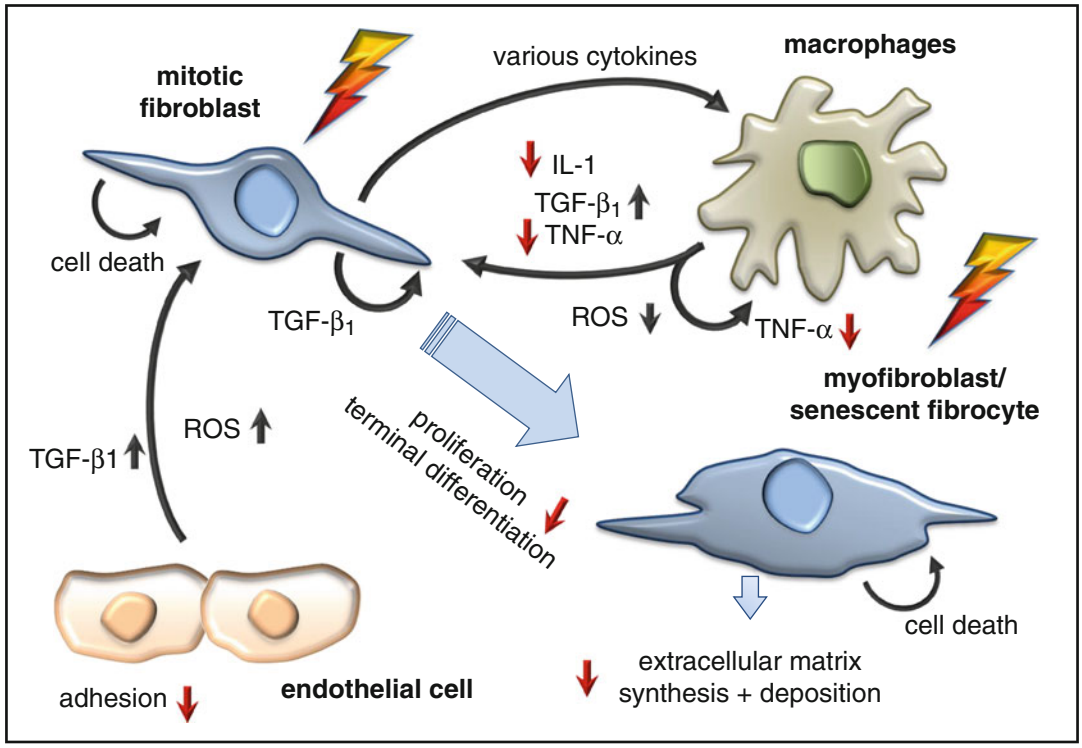

Fig. 45.1 Model of target cells and involved factors. Advanced model of target cells and factors involved in the therapeutic modulation of hyperproliferative/fibrotic benign diseases by a low-dose radiation therapy. Upon fibrotic activation by TGF-β1 and other factors, progenitor fibroblasts will be activated to form myofibroblast/fibrocyte that in turn increase deposition of ECM compounds. Ionizing radiation may interfere with this process by eliminating radiosensitive mitotic fibroblasts, forcing differentiation of fibroblasts, induction of free radicals, modulation of cytokine production and endothelial cell and macrophage activity. Abbreviations are given in the text

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46 Review of Radiation Therapy for Palmar and Plantar Fibromatosis (Dupuytren and Ledderhose Disease)

M. Heinrich Seegenschmiedt, Karin Piefel, and Thomas Schneider

Contents

46.1 Introduction

Palmar fibromatosis and plantar fibromatosis, called Dupuytren Disease and Ledderhose Disease (DD, LD), respectively, are chronic inflammatory and hyperproliferative connective tissue disorders which involve the palmar fascia of the hand and the plantar fascia of the foot, where they produce nodules, cords, and contractures; in addition, the overlaying subcutaneous fat and skin layers can be affected. These digitopalmar and digitoplantar alterations are part of a deforming and progressive, irreversible condition and part of a systemic connective tissue disorder (Enzinger and Weiss 1995), which is characterized by typical biochemical changes and additional fibrous deposits located at the dorsal PIP joint (forming knuckle pads), on the ear helix, the hand wrist, the elbow, and the penis forming a penile angulation (Peyronie disease). Although the tissue changes appear to have some pathohistological similarities, many studies and research efforts to identify a single cause of this generalized disorder have failed so far (Tomasek et al. 1999; Rudolph and Vande Berg 1991). Although numerous hypotheses exist about the disease onset and progression, the specific role of mesenchymal stem cells, fibroblasts, and myofibroblasts and the correlation with the clinical development of DD and LD are still not conclusively answered (Rödel and Seegenschmiedt 2016).

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Although the specific role and use of ionizing irradiation of hyperproliferative tissues are unfamiliar to or controversially discussed by hand surgeons, there is a much better and long-standing reputation due to new clinical studies in radiation medicine (Eng et al. 2006; Leer et al. 2007; Seegenschmiedt and Micke 2012; Seegenschmiedt et al. 2015). The impact and typical effects of radiotherapy using X-rays or photons and electrons or protons to inhibit proliferation of malignant tumor cells are well known and a widely accepted practice in oncology. In contrast, the application of ionizing radiation for nonmalignant or so-called benign conditions is far less known but supported by accepted clinical practice indications for radiotherapy of heterotopic ossifications, keloids, aggressive fibromatosis, and other proliferative disorders like the palmar and plantar fibromatoses addressed in this book.

46.2 Radiobiological Rationale

The radiobiological rationale for the use of ionizing radiation to alter the disease process in DD and LD is based on several radiosensitive target cells and biological mechanisms as discussed by Rödel and Seegenschmiedt in this book (2016). Table 46.1 summarizes the most important aspects.

Generally, the effects of ionizing radiation affect the tissue growth factor beta (TGFβ) and the proliferating fibroblasts and myofibroblasts at various stages in their disease process not only in the early phase (myofibroblast type I) but also in the later phase of the disease (myofibroblast types II and III). Figure 46.1 illustrates how large single doses of radiotherapy in the range of 8–10 Gy (ED) or fractionated lower-dose radiotherapy in the range of five times of 2–3 Gy (FD) transform the proliferating cell population into the nonproliferating postmitotic fibroblasts (PMF). The antiproliferative effect is highest in the earlier disease stages and lowest in the later stages.

Table 46.1 Radiosensitive targets and mechanisms in benign conditions

1. Proliferating *mitogenic fibroblasts/myofibroblasts* are radiosensitive cells (Rodemann et al. 1991; Rodemann and Bamberg 1995; Rubin et al. 1999)
2. Production of free radicals impair proliferative activity of fibroblasts (Murrell and Francis 1994)
3. Radiation exposure interferes with *growth factors* PDGF and TGFβ (Terek et al. 1995; Tomasek and Rayan 1995; Rayan et al. 1996; Tomasek et al. 1987)
4. Radiation exposure *reduces activated monocytes and macrophages* interacting with the inflammatory process and myofibroblast proliferation (Rubin et al. 1999)
5. Clinical experiences *with similar radiosensitive target cells/mechanisms:* (Seegenschmiedt et al. 2004)
(a) Intravascular hyperproliferation after arterial stenting (Crocker 1999; Tripuraneni et al. 1999);
(b) Keloid relapses after surgical excision (Suit and Spiro 1999; Kutzner et al. 2003)
(c) Relapses of recurrent pterygium (Smitt and Donaldson 1999)
(d) Growing experience with radiotherapy of Dupuytren Disease since the early 1950s (Finney 1955)

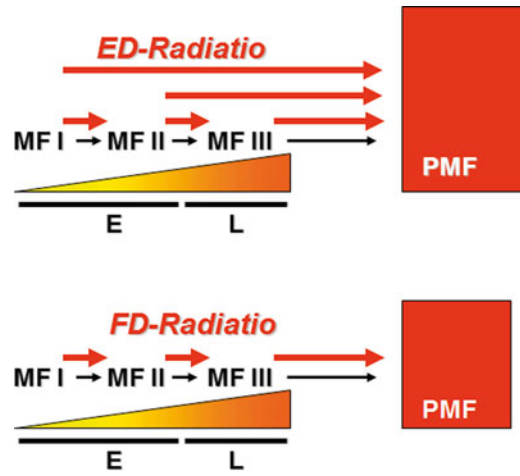

Fig. 46.1 Effects of radiation dose and radiation concept on proliferation of myofibroblasts (MF) are transformed from type I to type III myofibroblasts into nonproliferating myofibroblasts (PMF). Single high doses of radiotherapy (ED) are more effective than fractionated radiotherapy (FD). Earlier onset of radiotherapy (E) is more effective than later (L) (Figure reprinted from Warwick (2015))

46.3 Clinical Rationale for Radiotherapy

The course of DD comprises three disease phases which reveal different radiation sensitivities:

- The radiosensitive *hyperproliferative phase* (with increased number of fibroblasts, nodules, and early cord formation)
- The lesser radiosensitive *involutional phase* (with increased number of myofibroblasts in

diseased fiber bundles leading to cords and contractures)
- The radio-*in*sensitive *residual phase* (with collagenous fibers dominating the connective tissue)

Unlike in aggressive fibromatoses, for DD and LD no invasion of voluntary muscles occurs. DD and LD may slowly progress and stabilize for years, but rarely regress spontaneously. Without therapy the average progression rate is about 50 % within a period of 5 years (Millesi 1981). In LD, the slowly growing nodules and cords are rarely detected in the early phase, until dysfunction (walking difficulties, pain, tension, or pressure sensation) leads the patient to medical attention. In addition, the occurrence of concomitant knuckle pads and Peyronie disease in males supports the diagnosis (Donato and Morrison 1996).

The clinical course of DD and LD is dependent on the individual patient's disposition (Strickland et al. 1990). Spontaneous regression of DD is quite rare; moreover, slow progression may be interrupted by phases of stagnation; other cases rapidly progress within a very short time causing contracture-induced dislocation of digital joints in DD and walking difficulties in LD. Special subtypes are differentiated according to their characteristic clinical course, e.g., depending on comorbidities, like diabetes mellitus, or depending on the age at the disease onset or depending on the time course or uni- or bilateral affliction (McFarlane et al. 1990).

Radiotherapy provides a primary approach to the afflicted areas in the early stage of the disease, when other preventive or prophylactic methods are still unavailable.

46.4 Indications for Radiotherapy

Over the past decades, the use of radiotherapy (RT) has been more and more limited to the early and still proliferative phases of the disease where surgery plays no role and radiosensitive targets are still available. This excludes patients with "dormant disease" (which may last for years) and those with more advanced disease starting from a finger extension deficit of more than 30°; thus, only patients with "early progressive disease" who are usually characterized by multiple progressive nodules, fresh formation of a few cords, and/or presence of only a minor functional deficit (10–30°) may qualify for the implementation of radiotherapy to prevent further disease progression. Patients with "late progressive disease" with major functional deficits (>30°) do not anymore qualify for the use of RT. Typical clinical examples are shown in Figs. 46.2 and 46.3.

The indication for RT strictly follows the clinical staging, which is based on the amount of extension deficit of finger movement for DD (Tubiana et al. 1966) and the functional impairment due to involvement of the skin or the deep structures of the foot in LD (Sammarco 2001) (Tables 46.2 and 46.3).

46.5 Justification for Early Treatment

Despite decades of clinical and experimental research up to now, no cure is available for both DD and LD. All noninvasive and invasive treatments, including options like local injections with collagenase, application of systemic medication, performance of minimally invasive surgery including percutaneous needle fasciotomy, or open, radical open surgery, aim to prevent progression or to improve the impaired functional status. Moreover, in the very *early DD and LD stages*, a "wait and see" policy is always advised, as no conservative treatment has been proven effective. About two thirds of detected DD and LD cases will never progress to a stage where surgery is a final treatment option. Glucocorticoid injections may lead to regression but can also induce severe complications like atrophy at the injection site or rupture of tendons and have no long-term impact on disease progression (Ketchum and Donahue 2000). Without any therapy the clinical progression of DD is observed in about 50 % of patients after 6 years (Millesi 1981). This development is to be stopped by the early intervention using ionizing radiation. The gold standard for *advanced DD and LD* remains surgery, with the major goal of improving the finger function by reducing the contractures and thus restoring a disabled hand or foot function.

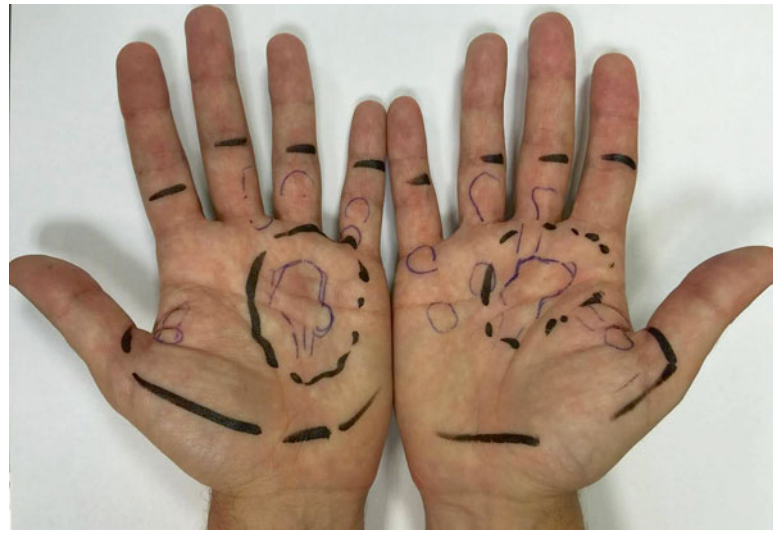

Fig. 46.2 Indication of radiotherapy for bilateral stage N bilateral Dupuytren Disease of stage N in a 67-year-old male; the dotted lines in the hand palm depict the region noted by the patient, while additional findings of nodules and cords have been detected after physical exam. The black outline shows the treatment area for radiotherapy

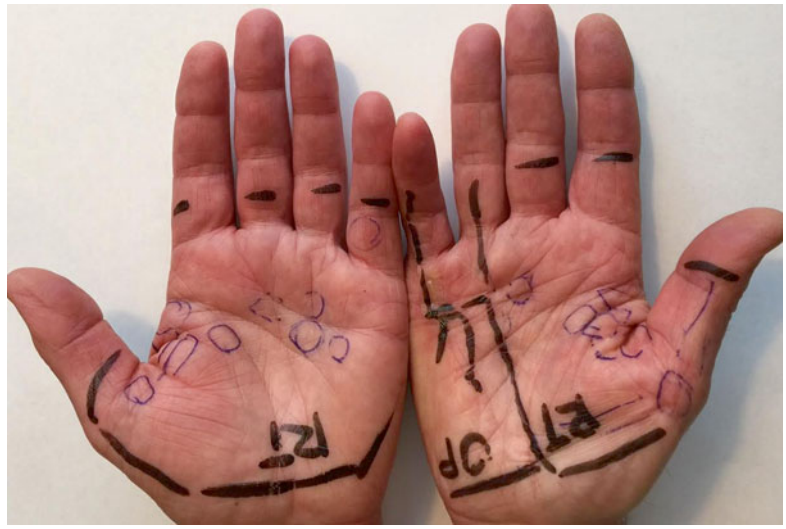

Fig. 46.3 Indication of radiotherapy for bilateral stage II Dupuytren Disease, stage II, postoperative in the right hand, and stage N in the left hand of a 63-year-old male; the right hand had three surgical procedures in the area of the ring and little fingers over the past 10 years; due to progression of nodules and cords in the unaffected left hand and the index and middle finger of the right hand, radiotherapy was applied to the not operated areas of the right hand and the untreated but progressive areas of the left hand (D1–D4). The black outline shows the treatment area for radiotherapy of the right hand palm

While hand or foot surgery is usually justified to improve a severe functional deficit (usually at stages I–II), RT always aims to prevent the progressive symptoms (formation of new nodules and cords; reduction of symptoms like pressure, itching, and sometimes pain) and to avoid future finger deviation and functional impairment (e.g., grip and spreading or holding functions of the fingers). However the implementation of radiotherapy implies the presence of radiosensitive target cells or biological mechanisms within the disease process for a successful interaction. Radiotherapy is effective for prevention of disease progression in early stages of DD (Keilholz et al. 1996; Adamietz et al 2001; Seegenschmiedt et al. 2001;

Table 46.2 Classification of Dupuytren Disease (DD) and RT indication

Stage	D1 (thumb)	D2–D5 (other fingers)	Points	RT indication
0	Neither nodule nor loss of abduction	No extension deficit No nodular or cord lesion	=0	No RT indication; no other treatments
N	Nodule without loss of abduction	Nodule without flexion contracture	=0.5	Early RT indication
N/1	Nodule without loss of abduction	Extension deficit of all finger joints equivalent 10° (-30°)	=0.5	Late RT indication
I	Abduction angle range 45–30°	Extension deficit of all finger joints equivalent 11–45°	=1	Surgical methods minimally invasive; collagenase, etc.
II	Abduction angle range 29–15°	Extension deficit of all finger joints equivalent 46–90°	=2	Minimally invasive and invasive procedures; collagenase, etc.
III	Abduction angle range 14–0°	Extension deficit of all finger joints equivalent 91–135°	=3	Minimally invasive and invasive procedures; collagenase, etc.
IV	Not defined	Extension deficit of all finger joints reaches more than 135°	=4	
R	Any status progression after previous surgical therapy			Possible postoperative RT indication under clinical investigation
	Maximum: 3 points	*Maximum: 5 × 4 points*	*=23*	*Tubiana score*

Table 46.3 Classification of Ledderhose Disease (LD) and RT indication

Stage	Stage	Definition	RT indication
I	Unifocal disease	*One nodule/cord* or circumscribed region involved w/o skin adherence or extension to the flexor sheath (plantar fascia)	No RT indication
II	Multifocal disease	*Several nodules/cords* or regions involved w/o adherence to skin or extension to flexor sheath (plantar fascia)	Early RT indication
III	Stage II plus deep extension in ONE direction (skin or foot muscle)	Several nodules/cords or *regions* involved with *deep extension* to EITHER skin (= III A) OR flexor sheath (plantar fascia) (= III B)	Early RT indication
IV	Stage II plus deed extension in BOTH directions (skin and foot muscle)	*Several nodules/cords* or *several regions* involved; with *deep extension* to skin (III A) AND flexor sheath (plantar fascia) (III B), i.e., stage III C	Late RT indication
R/post op	Recurrent stage, postoperative stage	Any status progression after previous surgical therapy	Individual RT indication under clinical investigation
Specific signs gait and pain	*Symptoms and functions*	*Nodules (N), cords (C), pain symptoms (P), other symptoms (S), walking disorder (W), dysfunction (D)*	*Other parameters salvage after failing multiple therapies*

Seegenschmiedt et al. 2012a) and LD (Seegenschmiedt and Attassi 2003; Grenfell and Borg 2014; Heyd et al. 2010; Seegenschmiedt et al. 2012b) with mild acute or late side effects.

There is a good radiobiological rationale for the long-term efficacy of the use of ionizing radiation on proliferating fibroblasts and myofibroblasts because they are radiosensitive cells;

ionizing radiation effectively impairs their proliferative activity by induction of free radicals which leads to a reduced cell density (Murrell et al. 1990; Murrell and Francis 1994); this can stabilize the disease as long as the proliferation dominates in early DD/LD stages N and I. However, in the later stages, the disease is already characterized by repair and contraction of fibrous tissue: ionizing radiation is ineffective in these tissues. *The major rationale is to use RT in early sensitive stages to avoid disease progression with later dysfunction that might require hand surgery.*

A careful physical examination of both hands and feet is needed and if possible with frequent follow-up to demonstrate any changes within a period of 3–6 months to establish whether the disease is progressing.

Figure 46.4 shows a 52-year-old male with progressive development of nodules and cords within one year follow-up and decision to provide radiotherapy for early stage N Dupuytren Disease.

Table 46.4 summarizes the different treatment indications depending on the disease stage and reveals the specific indication for radiotherapy in contrast to other therapies. There is much less choice of treatment for the early stages than in later stages of DD. Radiotherapy should be only indicated in progressive disease, when nodules and cords start to grow toward the situation where an initial angulation deficit occurs. Generally there are alternative conservative and surgical options available (Mafi et al. 2012). Actually we lack clinical studies, to answer whether radiotherapy may prevent early relapses after surgery for DD, while for LD some clinical studies suggest a possibly successful treatment option.

46.6 Documentation and Treatment Planning

Prior to the onset of RT, it is important to document the exact disease record including the family history, the professional activities, the additional disorders (like diabetes, etc.), and the course of disease in the specific situation. All details are documented in a questionnaire and special data format. All findings from the physical examination are documented together with a photograph of all involved extremities.

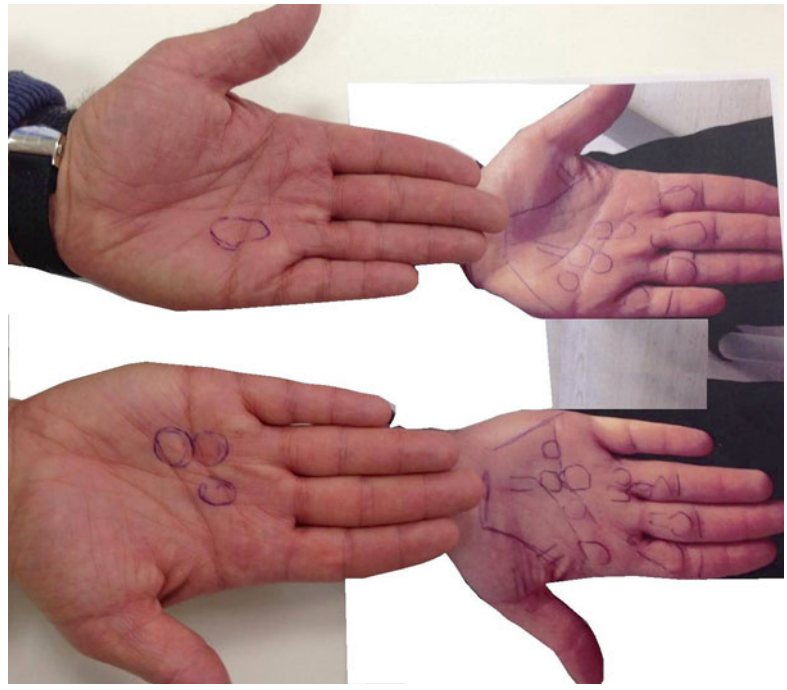

Fig. 46.4 Early stage without treatment and follow-up with treatment decision for radiotherapy. *Right*: left and right hand at first clinical visit 09/2013; *Left*: progression and treatment decision 12/2014

Table 46.4 Differentiation of treatment indications dependent on disease stage

Modified Dupuytren Tubiana stage (extension deficit angle; hand function)	N 0° Progressive nodes and cords; no deficit	N/I 0–10° Minor angulation deficit	I 10–45° Increasing angulation deficit	II 46–90° Disabling angulation deficit	III–IV >90° Major angulation deficit
Wait and see policy	Dormant stage without progress				
Radiotherapy	*Progress of nodes and cords in 3–6 months*	*Progress of minimal function deficit*	Progress up to 30° deficit		*possible postoperative use*
Minimally invasive surgery/needle fasciotomy	–	–	Progress beyond 30° deficit	Progress beyond 45° deficit	(+)
Collagenase injection	–	–	Progress beyond 30° deficit	Progress beyond 45° deficit	(+)
Open hand surgery	–	–	(+)	Complex situation	Extensive disease

Follow-Up: A continuous program of future prospective observations is implemented using direct periodical visits of the patients, telephone, or e-mail consultations to define the long-term outcome (remission, no change, progression) and decide on possible salvage secondary treatments which may include re-irradiation, surgery, or noninvasive procedures. Our definition of the follow-up intervals after completion of RT is as follows: 3, (6 and) 12, 36, and 60 months after the completion of RT, thereafter every year up to 10 years. During the follow-up period, photographic and functional reevaluation of your hand(s) or foot (feet) is essential. Physical examination should be done every second year up to 10 years.

46.7 Radiotherapy Treatment Protocols

Different dose protocols have been applied in the past with single RT doses usually ranging from 2 Gy to 10 Gy, the fraction numbers ranging from 4 to 10 sessions and the overall treatment time from 2 weeks up to several weeks or even months (Table 46.5). Sufficient dose is required to achieve a sufficient antiproliferative effect, which has been shown in keloid radiotherapy (Kal and Veen 2005). So far, from most published clinical studies, single-fraction doses of 3 Gy and total doses above 20 Gy appear to the most successful concepts, but only a few groups have compared different RT protocols within a controlled trial. Our group was the first to present a controlled clinical trial which compared a group of patients with no treatment versus two randomized groups of 21 Gy and 30 Gy, which were both applied using 3 Gy single fractions over two weeks (7 × 3 Gy) versus 3 months (two series of 5 × 3 Gy each). Both RT schemes were significantly superior to no therapy regarding disease progression and avoidance of later surgery (further details below) (Seegenschmiedt et al. 2012a).

Target volumes are shaped with lead cutouts (for electrons) or lead plates (for low-energy photons) depending upon the RT technique. Treatment setup is shown for Dupuytren Disease at an orthovoltage machine with 150 kV photons (Fig. 46.5a) and a Linac accelerator with 4 MeV electrons (Fig. 46.5b).

RT is sometimes given in the postoperative setting, when early relapse may impair the long-term outcome. In those instances not only the involved operated finger but also the other fingers and respective palmar fascia are treated (see Fig. 46.6a, b).

46.8 Clinical Experience and Outcome of Radiotherapy

More than 20 clinical studies conducted over the past 50 years have suggested that external beam RT may prevent disease progression in both DD and LD. However, these results have often been based on retrospective clinical studies with short follow-up, different indications, different patient selection criteria, different stages of disease, variable RT protocols, different criteria to evaluate clinical outcome, and variable follow-up periods. There are no direct comparisons within these studies or in comparison with parallel surgical series (Table 46.6).

At present, only a few clinical studies have sufficient patient and clinical data to enable reliable long-term conclusions. Some of these are described in the following sections.

46.8.1 The Erlangen Dupuytren Study

The first large German retrospective study from Erlangen (Betz et al. 2010) had been initiated as early as 1980 and was updated several times (Keilholz et al. 1996, Adamietz et al. 2001); thus, it is the first clinical report on a larger number of patients ($n=135$) with a very long median follow-up of up to 13 years for a total of 208 sites (i.e., hands).

This study provides very reliable data as a uniform RT technique was applied throughout the whole time course of the study. Similar to other studies, orthovoltage RT was applied in two separate courses of 5×3 Gy up to a 30 Gy total dose with a break of about 6–8 weeks. Only few patients (sites) were lost to follow-up, and the study could demonstrate a long-term effect on 123 (59%) sites which remained stable and 20 (10%) sites which even improved; only about one third of the treated population (65; 31%) progressed after the initial application of RT. The study found several important prognostic factors for a favorable outcome. Patients or sites with an early stage N remained stable or regressed in 87% and with stage N/I in 70%, while in more advanced stages (I–IV), the irradiated sites progressed in 62% (stage I) and 86% (stage II). Thus, a total of 66% were able to achieve long-term symptom relief. 31 % progressed either within the RT field only (14%) or outside the RT field only (3%) or within and outside the previously irradiated RT field (14%), respectively.

Moreover, the application of RT did prevent a possibly necessary surgical procedure or did not enhance any type of complications after hand surgery in case of a disease progression and required surgical procedures. Only in 32% of the irradiated sites some minor grade 1 late effects (minor skin atrophy, dry skin desquamation) were observed. Overall, no secondary malignancies were observed within or in the vicinity of the RT field. In summary, this study confirms the necessity for an early RT indication to achieve and maintain a long-term control, preserve excellent function of the affected hands, and avoid primary or salvage hand surgery.

Table 46.5 Applied radiotherapy concepts

RT concept	Total dose	Explanation	Current application
>3×10 Gy	30 Gy	Radium moulage with grip hold	Historical (not applied today)
>8×4 Gy	32 Gy	Dermatological orthovoltage RT 2 fractions of 4 Gy every 4 weeks	Only rarely applied today
>7×3 Gy	21 Gy	Orthovoltage or Linac RT 3 fractions per week over 2 weeks	Applied in randomized study
>10×3 Gy	30 Gy	Orthovoltage or Linac RT 5 fractions per week repeated after 12 weeks	Applied in randomized study
>10×2 Gy	20 Gy	Orthovoltage or Linac RT 5 fractions per week for 2 weeks	Routinely applied, but not tested in randomized study
>5×3 Gy	15 Gy	Linac RT 5 fractions per week for 1 week	In postoperative applications

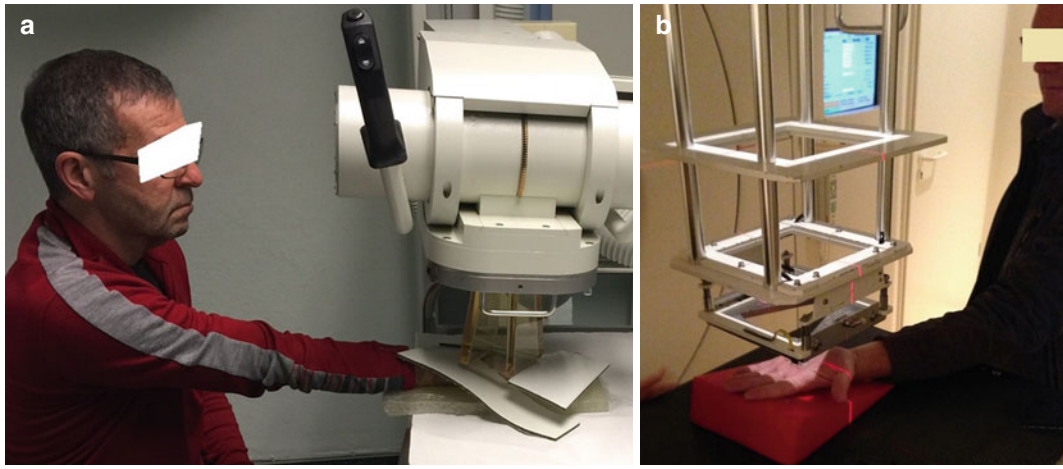

Fig. 46.5 (**a**) RT treatment with an orthovoltage machine (100–200 kV) using lead rubber plates to individually size the treatment portal. (**b**) RT treatment with a Linac accelerator with 4 MeV electrons

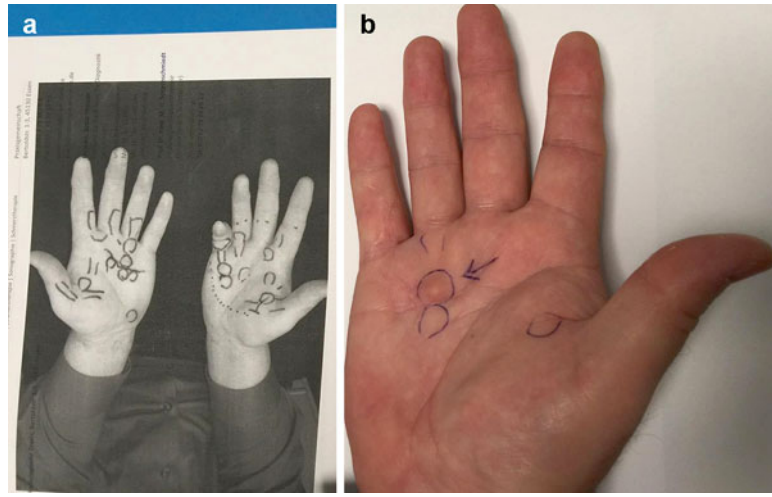

Fig. 46.6 (**a**) (Preoperative) and (**b**) (postoperative 2 years after surgery). (**a**) Shows the 90° angulation of D5 of the right hand in bilateral Dupuytren Disease in a 51-year-old male (musician) who had fasciectomy and was treated with one RT series (5 × 3 Gy up to 15 Gy). (**b**) Demonstrates the long-term follow-up at 2 years following surgery and radiotherapy with excellent functional status of D5 with almost no deviation and no progression in the others digits D1 to D4 of the right hand. The zigzag scar extends from the DIP joint of D5 to the middle of the palm; D4 shows a prominent and hard nodule in the palm (*arrow*)

46.8.2 The Essen Dupuytren Study

The German group from Essen performed the first controlled clinical trial to define the most effective RT dose (Seegenschmiedt et al. 2012a); parallel to the randomization, a control group of untreated patients was followed over the same time period.

From 1997 to 2009, 612 patients were referred to the clinic. 594 patients (356 M; 238 F) were followed for a minimum of 5 years up to a maximum of 17 years; mean follow-up was 11 ± 4 years. Up to this time, only 18 patients (3 %) were lost in FU. Due to the bilateral affliction in 268 patients, a total of 880 hands (sites) were available for long-term evaluation. The different

Table 46.6 Selection of clinical studies using radiotherapy for Dupuytren Disease

Authors, studies	Number of cases (n)	RT treatment: single/ total doses	Time of follow-up (FU)	Clinical results "stable" or "better outcome"
Finney (1955)	43	1000/1000–3000 r 400 mgE Ra moulage	–	15/25 (60 %) "good functional outcome"
Wasserburger (1956)	213	1000–3000 r (O) 400 mgE Ra moulage	12 mo.	Stad. I: 62/69 (90 %) Stad. II: 26/46 (57 %) Stad. III: 10/31 (32 %)
Lukacs et al. (1978)	158	4 Gy/32 Gy	–	Stad. I: 32/32 (100 %) Stad. II: 3/4 (75 %)
Vogt u. Hochschau (1980)	154	4 Gy/32 Gy	>36 mo.	Stad. I: 94/98 (94 %) Stad. II: 3/4 (75 %) Stad. III: 6/12 (50 %)
Hesselkamp et al. (1981)	65	4 Gy/40 Gy	>12 mo.	Total response: 43/46 (93 %)
Köhler (1984)	38	2 Gy/20 Gy	>12 mo.	Total response: 27/33 (82 %)
Herbst u. Regler (1985)	46	3 Gy/9–42 Gy	>18 mo.	Total response: 45/46 (98 %)
Keilholz et al. (1996, 1997)	142	3 Gy/30 Gy in 2 series with 5 × 3 Gy	>12 mo. >72 mo.	Total response: 126/142 (89 %) Progress: 13/57 (23 %)
Seegenschmiedt et al. (2000)	198	Randomized study: 3 Gy/21 in one series versus 30 Gy in 2 series	>12 mo.	Total response: 182/198 (92 %) Progress: 16/198 (8 %)
Adamietz et al. (2001)	176	3 Gy/30 Gy in 2 series	>120 mo.	Stad. N: 64/76 (84 %) Stad. N/I: 10/15 (67 %) Progress: Stad. I: 42/65 (65 %) Stad II/III: 13/15 (87 %)

disease factors were assessed, and the Tubiana staging was distributed as follows:

575 hands (65 %) with stage N (nodules/cords, no extension deficit)
158 hands (18 %) with stage N/I (≤10° deficit)
126 hands (14 %) with stage I (11–45° deficit)
21 hands (2 %) with stage II (46–90° deficit)

After clinical assessment and informed consent, a total of 101 patients with Dupuytren involvement of 141 hands voluntarily decided not to receive radiotherapy but opted for "watchful waiting." The remaining 511 patients with Dupuytren involvement of 739 hands were randomized for RT according to two different RT protocols:

Group A (258 patients/374 hands) received 30 Gy (2 series of 5 × 3 Gy, 12 weeks break)
Group B (253 patients/365 hands) received 21 Gy in one series within 2 weeks

The RT technique was similar to the Erlangen study by using orthovoltage RT (120 kV) photons together with an individual shielding of the uninvolved areas of the palm and fingers by lead rubber plates. The most relevant patient (age, gender, risk factors) and disease (number of nodules, cords, symptoms, and functional deficit) parameters were equally distributed between the control group and the two RT groups. The final evaluation was completed in November 2014. The primary end points were objective clinical progression and necessity of surgery. Secondary end points were side effects and objective parameters (number and size of nodules, cords) and patient's satisfaction.

Results: The local acute toxicity was very low and only temporarily for about 4–6 weeks in the two RT groups (25 % CTC 1°; 2 % CTC 2°); late radiogenic effects included the symptom of "dry skin" in 14 % (LENT 1); within the whole follow-up period, not a single ulcer or secondary cancer occurred in long-term FU. A total of 139 (19 %) sites showed remission of nodules, cords, or T

stage, while 390 (53%) sites remained in stable condition, which was the major objective of the use of RT.

Overall only 210 (28%) sites progressed and of those 129 (17%) required hand surgery. With regard to the different treatment groups, in the control group ($n=141$) the disease progression was observed in a total of 93 (66%) sites where hand surgery was required in 68 (48%) hands.

In comparison in group A (treated with a total dose of 30 Gy, $n=374$), only 19% of the sites showed signs of disease progression, and only 8% had a surgical procedure; in comparison in group B (treated with a total dose of 21 Gy, $n=365$), 26% sites developed progression, and 14% had a surgical procedure; the comparison between the control group and the two RT groups was highly significant ($p<0.001$); in addition, the RT concept of 30 Gy was more advantageous than the 21 Gy ($p<0.05$).

Moreover, while the number of nodules and cords decreased in both RT groups, in comparison the control group had an increase of at least two nodules and one cord ($p<0.01$). In addition, the Tubiana stage progressed in the control group significantly more often as compared to both RT groups ($p<0.01$). Overall, a total of 54 (7%) relapses occurred inside the RT portal, while 128 (17%) occurred outside the RT field, most often in the previously unaffected contralateral hand. In all progressed sites, surgical procedures after RT were possible without increased complications.

With regard to prognostic factors in uni- and multivariate analysis, the most important prognostic factors for progression were smoking (trend; $p=0.04$), symptom duration prior to RT beyond 1 year, Tubiana stage more than stage N, extension deficit not existing, and additional digital involvement present (all $p<0.05$). However, the most important factor was the use of RT (group A better than group B) as compared to the control without RT ($p<0.001$).

In summary, the systematic long-term clinical evaluation reached the time points of the Erlangen study; the acute side effects were as low as in the Erlangen study. The long-term side effects beyond 5 years of follow-up were lower with 14% LENT grade 1 and no LENT grade 2 or more, and no secondary cancer was observed in the long-term follow-up. Both RT schedules were superior to observation, and the 30 Gy arm appeared superior to the 21 Gy arm. Over 90% experienced no progression of the disease in the early DD stages N and N/I. RT did not increase the complication rate, even in cases when surgery became necessary for progressive disease (Seegenschmiedt et al. 2012a).

46.8.3 The Essen Ledderhose Study

Only a few clinical studies have been published with regard to RT for LD. The largest series from Essen (Seegenschmiedt et al. 2012b) summarized long-term outcome of 91 patients with 136 affected feet receiving RT; all had progressive nodules or cords, and 88 (97%) had additional symptoms (numbness, pain, other symptoms); 86 (95%) had walking problems due to pain. 35 ft had recurrent or progressive LD after surgery. Additionally, 67 patients (with 134 unaffected feet) served as control group without RT. Orthovoltage RT (125–150 kV) was applied with 5×3 Gy repeated after 12 weeks up to 30 Gy total dose. 6 patients (11 ft) progressed and of those 5 (7 ft) had salvage surgery, one with a longer healing period. 60 ft (44%) remained stable, 65 feet (48%) regressed with regard to nodules, cords, or symptoms, and of those, 35 ft had complete remission with freedom of all nodules, cords, and symptoms. Previous symptoms and dysfunction improved in up to 90% and patients' satisfaction improved in 81 (89%). Acute side effects (CTC 1° or 2°) occurred in 29 (21%) or 7 (5%) feet. Late sequelae (LENT 1°: dryness or fibrosis of skin) occurred in 22 (16%) feet. Grade 3 acute or late side effects were not observed. Patients without RT had significantly higher progression and surgical intervention rates. In multivariate analysis recurrent LD after surgery, advanced disease, significant symptoms, and nicotine intake were indicators of worse prognosis.

46.8.4 Other Ledderhose Studies

A PubMed review identifies seven studies describing the use of radiotherapy as primary treatment for fascial fibromatosis between 1946

and 2013. The literature indicates that radiotherapy can prevent disease progression and improve symptoms for early-stage disease, with low likelihood of significant toxicities.

A Dutch study explored the use of combined surgery and radiotherapy (de Bree et al. 2004). The Dutch Network and National Database for Pathology (PALGA) was consulted to establish the true incidence of plantar fibromatosis. A total of 9 patients (with 11 ft involved) with LD referred to one institution for recurrent LD and the role of postoperative radiotherapy as a prevention of recurrence was studied. Twenty-six operations were performed and postoperative radiotherapy was used in 6 cases. The use of plantar fasciectomy was associated with the lowest recurrence rate. However, after microscopically incomplete excision or excision of early recurrence (≤6 months) alone, all LD lesions recurred, while any recurrence was rarely observed with the use of adjuvant RT but was associated with significantly impaired functional outcome in 3 cases which may be related to the repeated surgery as well.

The use of RT after surgery may improve short- and long-term outcome, but the available clinical data are still limited. In one retrospective study, the relapse rate of Ledderhose Disease (LD) after plantar fasciectomy with or without postoperative RT was evaluated over three decades (van der Veer et al. 2008): 27 patients with 33 affected feet (6 bilateral LD) underwent 40 surgical procedures and had a relapse rate of 60 %; radical surgery (total plantar fasciectomy) for primary LD achieved the lowest relapse rate (25 %), while limited local resection without RT resulted in the highest relapse rate (100 %); the existence of multiple versus single nodule (s) was also associated with a higher relapse rate. The relapse rate for primary LD after fasciectomy was reduced with postoperative RT. Total plantar fasciectomy alone was most successful particularly for primary LD, but still compromised by a 25 % relapse rate. Thus, RT may be a useful additive treatment for more complicated cases of LD treated with limited surgery.

In contrast to the postoperative use of RT, the retrospective study from Frankfurt/Offenbach (Germany) confirmed the excellent remission and local control rate of primary RT for LD with pain remission and improved gait (Heyd et al. 2010). The study compared two schemes (10×3 Gy or 8×4 Gy) and megavoltage electron or orthovoltage RT techniques but found no difference in treatment outcome. After a median follow-up of 2 years, none of the cases had progressive nodules and cords or increase of symptoms. Complete remission was achieved in 33 % (11 sites), partial remission was attained (reduced number and size) in 55 % (18 sites) and, 12 % (4 sites) remained unchanged but had no surgery in follow-up. Pain was relieved in 63 % and gait improved in 73 %; 92 % of the patients were satisfied with the outcome.

In an Australian study, six consecutive cases of early-stage fascial fibromatosis were treated with radiotherapy at the Adelaide Radiotherapy Centre between July 2008 and May 2011 and analyzed. All six cases regressed or showed a reduction of symptoms following radiotherapy, and the treatment was well tolerated with minor toxicities. Median follow-up for the case series was 38.5 months (Grenfell and Borg, 2014).

At the University of Virginia Richmond, outcomes after electron radiation treatment for early-stage Dupuytren and Ledderhose were reported. From 2008 to 2013, 44 patients with early-stage MD or LD received RT which encompassed the involved clinically defined targets and areas (skin changes, cords, nodules) with at least 1.5 cm margins. En face electrons (6–12 MeV) and bolus (0.5–1 cm) were selected individually. Outcomes are reported for patients who participated in an institutional review board-approved standardized questionnaire and chart review. Thirty-three patients received 66 treatments (45 hands/15 ft and 6 re-irradiations). Most frequent dose schemes were 21 Gy (3 Gy in 7 fractions) and 30 Gy (3 Gy in 10 fractions with 6- to 8-week breaks after 15 Gy). Median time to follow-up survey was 31 months. Disease progression at any location within or outside the RT treatment field occurred in 20 of 33 patients (61 %). Fourteen of 60 sites (23 %) developed in-field progression, but 4 sites were successfully re-irradiated with final local control in 50 of 60

sites (83 %). RT improved pretreatment symptoms of pain with strain at 30 of 37 sites (81 %) and itch/burn sensations at 17 of 21 sites (81 %). There were no reported grade ≥2 late toxicities even with re-irradiation. Patient reported overall success with treatment was 31 of 33 patients (94 %). Electron RT was a very effective therapy that stabilized or improved symptoms in the majority of patients. Re-irradiation can be considered as a treatment option for in-field progression. Patients report minimal toxicity and a high rate of satisfaction with treatment (Schuster et al. 2015).

Conclusions

In summary, RT for early-stage DD and LD has not only a strong radiobiological rationale, but has also shown to be a very effective treatment with acceptable acute and late toxicity in long-term follow-up for the prevention of the disease in early stages. Moreover, the exposure to 30 Gy RT dose does not increase the surgical complication rate when surgery becomes necessary in case of a later disease progression. The reported results from a limited number of studies of RT with long-term follow-up appear to be better than any reported surgical series with long-term follow-up. These findings should encourage further recruitment of patients into prospective RT studies with long-term evaluation and comparison with established minimal and or open surgical techniques. Ongoing clinical trials of collagenase injection for single DD nodules may compete with the indication for radiotherapy in the early stage of DD, depending on long-term results.

Thus, our recommendation is to apply routinely RT for early stages of DD and LD as the first noninvasive therapeutic approach within the first 1–2 years after diagnosis when clinical progression has been confirmed after an observation period of at least 3–6 months. The best established and clinically approved radiotherapy concept is 10 fractions of 3 Gy single dose split into two series of each 15 Gy within 3 months.

While many clinical surgery studies provide outcome data with less than 5-year follow-up, longer follow-up is critical when evaluating RT for possible long-term failure, compromised surgery after recurrence following RT, and potential late effects like radionecrosis (Falter et al. 1991; Loos et al. 2007; Weinzierl et al. 1993) or carcinogenesis (Jansen et al. 2005; Trott and Kamprad 2006). None of these criticisms have been confirmed by any controlled clinical study. And despite the fact that skin cancer is an increasing threat in older individuals exposed to sun, so far there is no single case in the literature reported about the development of a malignant tumor in the radiation portal after the application of RT for DD.

In addition, the use of RT after surgery could be explored in controlled clinical studies to find out whether RT could help to prevent early relapses after minimal invasive or open hand surgery.

Conflict of Interest Declaration The authors have no conflict of interest to declare.

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Splinting as a Therapeutic Option in Dupuytren Contractures

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Ilse Degreef and Annelien Brauns

Contents

47.1 Introduction

Dupuytren contractures are still largely treated with fasciotomy, whether with needles, surgery, or enzymatic injections. Rehabilitation is challenging and both intraoperative and postoperative complications are not uncommon. Moreover, recurrent contracture after treatment can occur in up to 60 % after fasciectomy, depending on the follow-up and the definition of recurrence in the numerous outcome reports (Verjee et al. 2009). Additionally, recurrence is unpredictable and can result from Dupuytren Disease or postoperative scarring, which cannot always be clearly distinguished (Dias et al. 2013). Postoperative splinting is often used and even more debated, but literature about splinting as a nonsurgical treatment is limited.

47.2 Myofibroblast Response to Mechanical Stress

The active contracting tissue in Dupuytren Disease consists of myofibroblasts, very similar to scar tissue formation (as in burns). These cells are more profusely present in the nodules, although cords can contain numerous myofibroblasts as well (Verjee et al. 2009). In vitro experiments report that these cells respond to mechanical stress (Citron and Hearnden 2003). Compression can induce apoptosis of the myofibroblasts (Reno et al. 2003).

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47.3 Translational Research

Because of recurrence after surgery and associated morbidity, research on noninvasive techniques is needed. Basic research on Dupuytren myofibroblasts improves our understanding of their primary role in disease development and progression, even though the actual cause or triggers remain unclear. Being responsible for progression of Dupuytren Disease and recurrence after surgery, myofibroblasts are a primary target in translational research. Transforming growth factor β (TGF-β1) is a potent inducer of myofibroblast differentiation in response to external mechanical forces (Bisson et al. 2009). Mechanical stretch causes upregulation of various growth factors and their receptors such as TGF-β1. Mechanical tension may therefore stimulate the myofibroblasts and worsen the contracture. An inadequate application of tension load such as stretching exercises may be counterproductive to Dupuytren contractures and even accelerate the progression of deformity (Brandes et al. 1994). Similar processes are also seen in burn scar tissue formation: granulation tissue subjected to increased mechanical tension produces hypertrophic scars by inhibiting apoptosis and differentiation of fibroblasts to myofibroblasts (Junker et al. 2008; Sarrazy et al. 2011).

On the other hand, the biomechanical effect of continuous extension on Dupuytren myofibroblasts generates an increase in enzyme activity to depolymerize collagen fibers (Bailey et al. 1994; Brandes et al. 1994). Increased levels of MMPs (metalloproteinases, remodeling enzymes of collagen tissue) in Dupuytren tissue therefore suggest a positive effect of continuous tension (Verhoekx et al. 2013). Neoformation and reorientation of these collagen fibers lead to softening of the tissue and loss of tensile strength which allows straightening of the fingers (Bailey et al. 1994; Brandes et al. 1994).

47.4 Compression or Traction Splinting

These lab findings support the translational idea of corrective splinting in Dupuytren contractures. Moreover, burn scar treatment is similarly based on continuous pressure and silicone padding.

Today, splinting is mostly used after fasciotomy of Dupuytren contractures. The reason for using splints posttreatment is that they provide low-load continuous forces to maximize finger extension, maintain correction, and prevent scar contracture. Decisions regarding the indications for splinting and the splinting regimen are based on clinical experience due to insufficient quality evidence about the actual efficacy of splinting (Larson and Jerosch-Herold 2008). A dogma on splinting being inefficient has persisted (Townley et al. 2006).

47.5 Single-Center Experience

At our hand unit, splinting has been the standard of care after segmental fasciectomy for decades and after enzymatic collagenase treatment since its introduction 5 years ago. Dynamic extension splinting for 3 months after treatment has been practiced for over 25 years. However, for 5 years, compression splinting was gradually developed and introduced as preoperative treatment option (Fig. 47.1). An interface pressure of 18 mmHg is achieved if compression splints are tightened correctly with a silicon layer. A recent randomized controlled trial comparing traction versus compression splinting in 30 patients with a high fibrosis diathesis demonstrated that an intense splinting regimen significantly reduced the flexion contracture with a mean of over 45° in compression splinting and over 30° in traction splinting (Fig. 47.2). The patients better tolerated compression splinting than traction splinting (report submitted). Compression also softened the nodules. Traction splinting regularly caused pressure sores and pain, especially in 5th proximal interphalangeal (PIP) joint contractures. Successful splinting can delay or even avoid the need for surgical intervention. In the light of socioeconomic costs, this low-cost treatment of a widespread disease may have a significant impact. To reduce contractures, splinting was needed for 20 h a day, and to maintain results (in evolving contractures, active disease), nighttime splinting appeared sufficient.

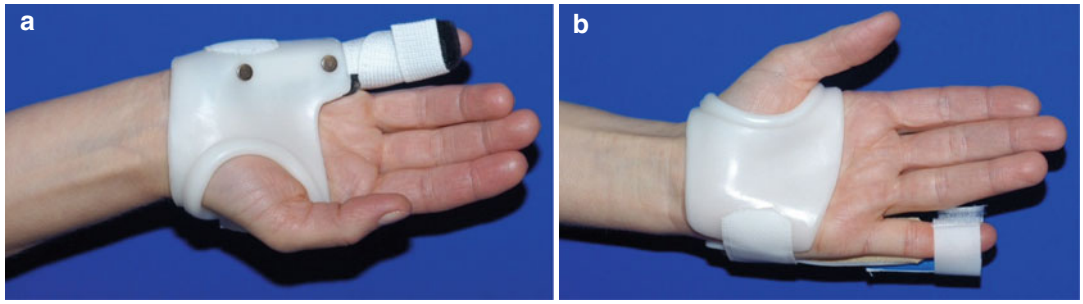

Fig. 47.1 (**a**): Compression splint in 5th ray; (**b**) traction splint in 5th ray

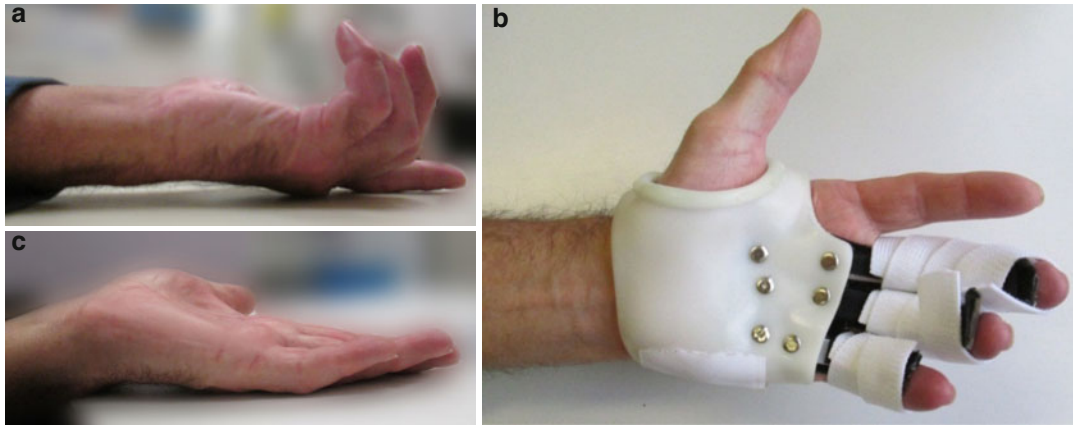

Fig. 47.2 Illustrative case of a satisfying result after 3 months of compression splinting. (**a**) Pretreatment, (**b**) compression splint, and (**c**) after 3 months of 20 h a day of splinting

47.6 Other Reports on Corrective Splinting

Only few reports are available. Larocerie-Salgado and Davidson developed a volar hand-based nighttime extension splint combined with physiotherapy (stretching and massage) on PIP joint flexion contractures. After one year he reported a significant improvement of 15° in mild contractures in 13 patients (Larocerie-Salgado and Davidson 2012). Meinel developed a glove with static insert on the extension site and palmar silicone bed. In contrast to our splinting regime, this glove splint was prescribed after percutaneous needle fasciotomy and is worn at nighttime for 6 months. He mentioned a personal experience with lower recurrence risk and clinical remodeling (Meinel 2011). Glasgow et al. demonstrated that splinting at least 12 h a day reduced traumatic digital contractures in a short period of time (3 months), even without surgery (Glagow et al. 2003).

47.7 Burn Scar Research

This idea of treating Dupuytren Disease by compression is today's golden standard in hypertrophic burn scar management Chang et al. (1995). There is no available clinical research on the effect of compression on Dupuytren nodules. Hypertrophic and keloid scars are similar fibro-proliferative disease processes as Dupuytren Disease (Townley et al. 2006). In normal wound healing, granulation tissue disappears after epithelialization through a massive apoptosis of myofibroblasts. This wave of apoptosis lacks in fibro-proliferative disease (Gabbiani 2003). As mentioned earlier, the activity of myofibroblasts depends on the mechanical environment (Sarrazy et al. 2011). Several nonsurgical

treatments have been proposed for hypertrophic and keloid scars, but only 2 have properties that induce mechanical forces on the scar: silicon sheets and compression therapy. The effect of compression therapy has been proven clinical (60–85 % success ratio) and histological, but the mechanisms responsible for hypertrophy remission following compression are not well understood (Fraccalvieri et al. 2012). Pressure therapy creates a localized hypoxia, which results in fibroblast degeneration and collagen breakdown (Worrell 2012, Yigit et al. 2009). An in vitro study on the effect of mechanical compression on hypertrophic scars demonstrated apoptosis in the derma of hypertrophic scars, twofold higher as compared to normal scar tissue (Reno et al. 2003). A prolonged compression can restore the cell organization as in normal scars and trigger myofibroblast apoptosis (Sarrazy et al. 2011).

47.8 Pressure and Silicon

There is discussion about the optimal amount of pressure. Most authors suggest a minimal interface pressure (pressure between the skin and splint) of 25 mmHg, but this is not evidence based (Macintyre and Baird 2006). The effect of pressure of 20 mmHg on fibroblasts in burn scars during 18 h causes an inhibition of fibroblasts and a decrease of TGF-β1, and a minimum of 20 h pressure splinting a day is advised (Sarrazy et al. 2011).

Silicon sheeting also is an imperative element in scar treatment and is generally well tolerated. The sheet must be worn for at least 12 h per day for 2–3 months to be effective (Berman et al. 2007). The combination of continuous compression with a silicon layer is a good method to manage keloid scarring and may thus be considered in Dupuytren Disease as well (Fraccalvieri et al. 2012). The challenge of traditional compression therapy in managing scarring or Dupuytren Disease is the ability to adequately fit the splint to the impaired area. It is therefore important to see the patient at regular intervals to adjust the splint to fit the achieved extension of the finger. A perfect contact between the skin and splint, especially at the nodules, is extremely important for reliable outcome.

Conclusion

Compression splinting should be considered as nonsurgical treatment in Dupuytren Disease, particularly in the case of palpable, visual, and in some cases even painful nodules. The use of splinting as a noninvasive, low-risk, low-cost treatment in primary or recurrent Dupuytren contractures may be a viable option. Both compression and tension splints can be effective in reducing the finger contractures, but compression therapy is better tolerated. A splinting regime of 20 h a day for 3 months is efficient in both early proliferative untreated hands as aggressive postsurgery recurrence disease. Long-term effects of tension and compression on Dupuytren nodules need more investigation, and the role of splinting in prevention of contractures in the long term is yet unclear.

Conflict of Interest Declaration No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this monocentric article, which is of academic interest only.

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Treatment Options for Patients with Adhesive Capsulitis (Frozen Shoulder)

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Marie A. Badalamente

Contents

48.1 Introduction

Adhesive capsulitis is a common disorder which involves glenohumeral pain and loss of range of motion in the active and passive planes. This condition was called "periarthritis scapulohumerale" by DuPlay (1896). Adhesive capsulitis is also commonly termed "frozen shoulder." This terminology was coined by Codman in 1934. However, it was Neviaser (1945) who first used the term adhesive capsulitis. The consensus definition by American Shoulder and Elbow Surgeons is "a condition of uncertain etiology which is characterized by significant restriction of both active and passive shoulder motion that occurs in the absence of a known intrinsic shoulder disorder" (Matsen et al. 1993; Zuckerman et al. 1994).

Other conditions can lead to the presentation of patients with a stiff and painful shoulder. These other conditions include, but are not limited to, tears of the rotator cuff, glenohumeral and acromioclavicular arthritis, calcific tendonitis, and bicipital tenosynovitis (Neviaser 1983). It is essential that accurate diagnosis of adhesive capsulitis be made in contrast to other conditions as treatment approaches differ.

48.2 Demographics and Classification

Adhesive capsulitis is reported by many investigators to affect approximately 2–5 % of the general adult population (Bridgman 1972; Wolf and Green 2002). Most commonly, adhesive capsulitis is known to affect women aged between 40 and 60 years preferentially over men (Bridgman 1972; Hand et al. 2008). Both shoulders may be affected by adhesive capsulitis, and usually the contralateral side is affected years after the onset of symptoms in the first shoulder (Hand et al. 2008; Reeves 1975; Shaffer et al. 1992). Most

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commonly, adhesive capsulitis does not affect the same shoulder more than one time.

With regard to the classification of adhesive capsulitis, treating physicians use the term primary or secondary. Primary adhesive capsulitis is defined as clinical presentation of no findings on history or radiologic examination to explain the onset of the disorder. In contrast, secondary adhesive capsulitis is defined from known causes of stiffness and loss of range of motion such as shoulder trauma or surgery or even post mastectomy.

48.3 Association with Comorbidities

Adhesive capsulitis can also commonly occur in patients with certain medical comorbidities. There is a very strong correlation between diabetes and adhesive capsulitis (Bridgman 1972). This report observed 10.8 % incidence among 800 diabetic patients versus only a 2.3 % incidence in 600 non-diabetic patients. Also, in diabetic patients, the rate of bilateral frozen shoulder is increased. Other medical comorbidities have also been found to have a higher incidence of adhesive capsulitis. These include thyroid disease, cardiac disease, and certain neurologic conditions such as Parkinson disease, stroke, and aneurysm surgery (Wohlgethan 1987; Bowman et al. 1988; Riley et al. 1989; Tanishima and Yoshimasu 1997; Lo et al. 2003).

There is a known correlation between adhesive capsulitis and Dupuytren Disease (Bunker and Anthony 1995; Smith et al. 2001). Smith et al. (2001) stated that Dupuytren Disease is over eight times more common in patients with adhesive capsulitis compared with the general population. This commonality potentially relates to the similar pathobiology of both adhesive capsulitis and Dupuytren Disease. Evidence supports that the pathobiology of adhesive capsulitis involves thickening and contracture in a fibrotic process of the inferior capsule (Wiley 1991). This involves contracture of the rotator interval, coracohumeral ligament, and anterior capsule which severely restricts the range of motion of the shoulder. It is also well known in Dupuytren Disease that a fibrotic process mediated by myofibroblasts produces both type 3 and type 1 collagen and leads to the formation of cords which cause flexion contracture. However, in adhesive capsulitis, it is thought that there may be a combination of synovial inflammation and shoulder capsular fibrosis. Interestingly, many of the growth factors causing fibrosis in both disorders share a commonality. These include such entities as transforming growth factor beta, platelet-derived growth factor, tumor necrosis factor gamma (Rodea et al. 1997), and the Wnt/beta-catenin pathway (Raykha et al. 2014). Degreef et al. (2008) have also reported that 45 % of female patients diagnosed with Dupuytren Disease also had adhesive capsulitis.

48.4 Duration

Adhesive capsulitis may have a long and painful, debilitating course. Investigators usually refer to a course of a continuum of three stages (Reeves 1975). Hannafin and Chiaia (2000) reported on a histologic classification throughout the various stages of adhesive capsulitis. Generally, it is believed that the disorder begins in the painful or so-called freezing stage in which patients have stiffness. The pain usually precedes the restriction of glenohumeral motion. This phase may last between 10 and 36 weeks. The second stage is the stiff or "frozen" stage in which the pain somewhat decreases, but there is a continual reduction in active and passive range of motion. This stage can be anywhere between 4 and 12 months. The last, recovery or "thawing" stage constitutes a gradual improvement of shoulder range of motion and function and may last from 5 to 26 months. The full course of adhesive capsulitis is reported to last anywhere from 1 to 3.5 years with a mean of about 30 months, but this is disputed and others have described a longer and more protracted course in many patients (Shaffer et al. 1992).

48.5 Treatments: Conservative and Surgical

With regard to conservative treatment of adhesive capsulitis, Jain and Sharma (2014) have published a systematic computer database review of 2,917 articles from the published literature. Only

39 of these articles were deemed to be useful based on levels of scientific evidence. The conclusions of this report recommend that physical therapy (therapeutic exercises) and joint mobilization are strongly recommended for reducing pain, improving range of motion and function in patients with stages 2 and 3 adhesive capsulitis. Also, low-level laser therapy was suggested for pain relief and moderately suggested for improving function but not recommended for improving range of motion. Corticosteroid injections were thought to be most useful in stage 1 adhesive capsulitis. Other therapies were reviewed for short-term pain relief, and the reader is directed to this systematic review article for a more in-depth evaluation of these lesser used therapies.

Other more invasive treatments, such as hydrodilation and nerve blockade, have been used to treat adhesive capsulitis (Jones and Chattopadhyay 1999; Dahan et al. 2000; Callinan et al. 2003). Hydrodilation was first described by authors in the mid-1960s (Andren and Lundberg 1965). This method seeks to rupture contracture of the shoulder capsule by distention of the joint with large amounts of normal saline solution.

With regard to surgical measures used to treat adhesive capsulitis, a review article has been recently published (Grant et al. 2013) in which a systematic review of databases was undertaken to compare manipulation under anesthesia and arthroscopic capsular release. Only 22 studies, 21 of which provided only level IV evidence, were included. Nine hundred eighty-nine patients were included in this comparison, and nine studies evaluated manipulation under anesthesia and 17 studies evaluated capsular release. The conclusion of this well done systematic review was that, overall, the quality of evidence available was low and that the data demonstrated little benefit for a capsular release instead of, or in addition to, manipulation under anesthesia. Finally, the conclusions were that high-quality studies are required to definitively evaluate the relative benefits of these procedures. Furthermore, these procedures are undertaken usually in recalcitrant primary or secondary adhesive capsulitis where patients have had the disorder for > six months or longer. Open surgical release for adhesive capsulitis is at the present time considered a historical treatment option (Ozaki et al. 1989).

Despite either conservative or surgical treatments, one study (Shaffer et al. 1992) has reported that after a mean seven years follow-up, 50 % of patients still had residual pain and/or loss of range of motion.

48.6 Clinical Trials of a New Treatment Method

Given the long, painful and protracted course of the many conservative therapies and surgical therapies for adhesive capsulitis, it appears that study of newer treatment methods is warranted. Toward this end, we have undertaken US Food and Drug Administration-regulated clinical trials of collagenase *Clostridium histolyticum* (CCH) injection (s) for adhesive capsulitis (Badalamente and Wang, 2006, 2009). The rationale for these studies was the similar pathobiology of collagen-mediated fibrosis between Dupuytren Disease and adhesive capsulitis. First, an injection method was developed to deliver an extra-articular injection to the anterior shoulder capsule. The injection site is midway between the tip of the coracoid and the bicipital groove (Fig. 48.1). The needle for injection is a blunt-tipped "Sprotte" needle which is not capable of penetrating the anterior capsule injection site nor the intra-articular joint space.

The site of injection is midway between the tip of the coracoid and the bicipital groove.

Next, the safety and efficacy of injectable collagenase *Clostridium histolyticum* was evaluated for the treatment of adhesive capsulitis. A small, randomized, double-blind, placebo-controlled, single-injection, dose-response, pilot study was conducted and followed by an open-label extension study. Sixty patients, 47 women and 13 men, were evaluated. Mean age was 52 ± 8 years, and mean duration of adhesive capsulitis was 17 months. Patients were randomized to receive a single injection of 0.5 ml placebo (physiologic saline and 2 mM $CaCl_2$) or 0.145, 0.29, or 0.58 mg collagenase diluted in placebo solution to the same volume. Extra-articular injection was

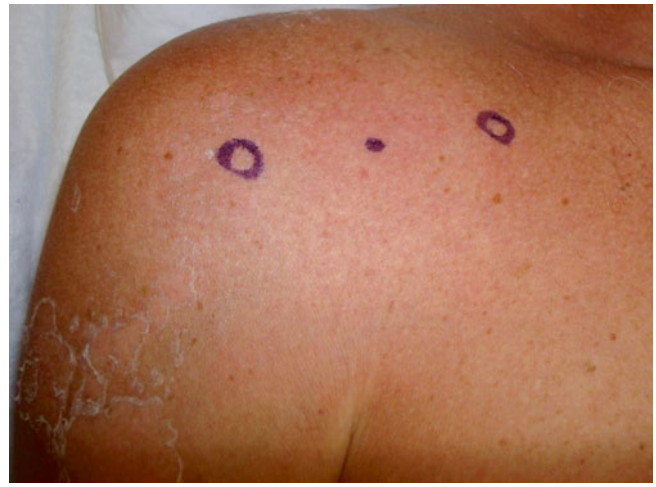

Fig. 48.1 Anatomic landmarks for CCH injection

directed at the anterior shoulder capsule in the supine position. Shoulders were serially evaluated for 30 days for range of motion in all planes. Outcome measures (function score, pain score, strength, and stability) were obtained using an American Society of Shoulder and Elbow Surgeons evaluation form. At 30 days postinjection, patients could receive up to 4 open-label 0.58 mg collagenase injections if active elevation was not improved to 160°. Long-term follow-up was up to 60 months. Results from the double-blind phase (one injection) demonstrated significant improvements from baseline in 4 measures of shoulder motion (active elevation, active external rotation, passive external rotation, and function) with collagenase (0.29–0.58 mg) compared with placebo (ANOVA, $P<0.05$). In most patients, one injection was not sufficient to restore normal motion and function. Within 30 days after the last open-label phase injection (injection #2, #3, #4) of 0.58 mg collagenase, shoulder motion, function, and pain were comparable to normal values. It appeared that shoulders with more severe limitation of active elevation at baseline required a greater number of collagenase injections. These data suggest that treatment with one or more injections of collagenase may improve shoulder motion, function, and pain in patients with adhesive capsulitis (Badalamente and Wang, 2006). The treatment was well tolerated, and at 60-month follow-up, there were no recurrences.

The next study sought to refine the anterior shoulder capsule injection method using ultrasound guidance.

Ten normal, healthy volunteers were enrolled. There were 8 females and 2 males, mean age 44.7 + 7.2 years. For anterior injection, subjects were supine, and the arm was passively externally rotated with the elbow at the side to 20°. The anterior shoulder area was washed with chlorhexidine prep solution. Landmarks were identified by palpating the bicipital groove and the coracoid process. These sites were marked with a sterile surgical marker pen. The injection site was midway in the coronal plane between these two landmarks.

Next, a local anesthetic of 1 % lidocaine solution in 10 ml was injected subcutaneously and therefore extra-articularly with a 20-gauge, 1 ½ inch needle at the midway point between the defined landmarks. This needle was placed perpendicular to the skin. Five minutes was timed to allow for sufficient lidocaine local anesthesia. The ultrasound probe was placed near the injection site. Next, 10 ml sterile saline was injected using the same needle track as was used for lidocaine anesthesia but using 22-gauge needle (Sprotte needle). All subjects chose to have the non-dominant side injected. Therefore, there were 8 injections to the left shoulder and 2 to the right shoulder.

Ultrasound images were recorded in a serial fashion. First, a posterior image was taken prior to

anterior Sprotte needle insertion. When the saline was introduced via the Sprotte needle, the timer was activated. The timer was stopped only when no saline could be seen on the anterior ultrasound images. Finally, a posterior ultrasound image was taken with the subject's on their side to assure that no saline was visible. The ultrasound imaging of the saline injection itself was performed (Fig. 48.2). The saline fluid remained anterior to the shoulder capsule (also confirmed by the posterior imaging) and extra-articular in all ten subjects. Specifically, nine of ten subjects showed a bolus (pocket) of saline fluid deep to the subscapularis tendon. In the remaining one subject the saline was seen on the anterior surface of the subscapularis. No saline fluid was visible in the glenohumeral joint space by anterior or posterior imaging. This study showed that 10 of 10 subjects who received saline injection to the anterior shoulder using only topographic landmarks as a guide resulted in extra-articular placement of the saline fluid. Palpation of the bicipital groove and the coracoid process were the landmarks used for injection. This injection technique is simple and reliable.

A phase 2a, open-label, controlled, dose-ranging, multicenter study was then designed to assess the safety and efficacy of collagenase *Clostridium histolyticum* (CCH) injection (s) compared to an exercise-only control group in patients with stage 2 (frozen) unilateral idiopathic adhesive capsulitis (AC).

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 $\geq 60^0$ in all planes and a deficit of $\geq 30^0$ 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 0.58 mg 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

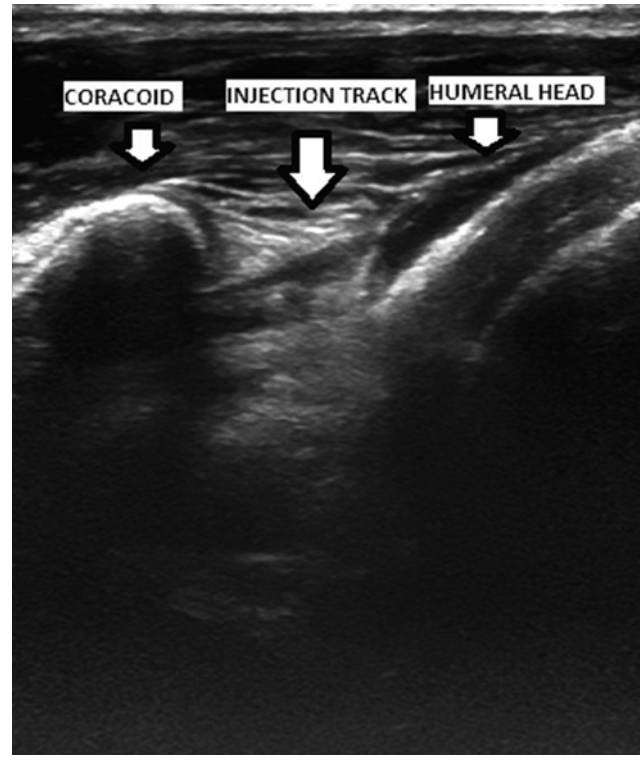

Fig. 48.2 Ultrasound image of the injection track midway between the tip of the coracoid and the bicipital groove

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.

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.

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 studies (Badalamente and Wang, 2006, 2009) and CCH use in other indications. Further clinical trials are ongoing to evaluate the potential merit of CCH in patients with adhesive capsulitis. This less invasive method holds promise as a new treatment for adhesive capsulitis with hope for reducing the pain and loss of shoulder motion in patients from years to only a few months.

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International Patient Survey (Part 2: Ledderhose Disease)

49

Anne Schurer, Gary Manley, and Wolfgang Wach

Contents

49.1 Introduction

Ledderhose Disease, also known as plantar fibromatosis or 'Dupuytren of the foot', consists of fibroma in the plantar fascia, usually, but not exclusively located on the medial part under the arch of the foot. The disease was named after the German physician Georg Ledderhose who described it in his publications in 1894 and 1897. In 1894 Ledderhose called it a fasciitis without linking to Dupuytren Disease in the hand, as none of his patient had hand symptoms (Ledderhose 1894). All 10 patients had developed pain and nodules in the plantar fascia after having an injury to the foot or having a plaster cast or splint applied to their lower leg. However, after examining some of the nodules histologically, he realized that the same cell types were found in the plantar as in the palmar fascia nodules. By 1897, he had seen 50 cases, some even with contracture of the fascia (Ledderhose 1897). Though spontaneous regression was observed, this did not happen often, and Ledderhose concluded the condition was the same as Dupuytren Disease. Guillaume Dupuytren himself had been aware of the foot-related disease and had promised to discuss it ('When opportunity presents, we shall speak of retraction of the toes, which is also caused by a crisping of the plantar aponeurosis' (Dupuytren 1832)) but died before he had the chance.

Research since then has been case studies mainly with low number of patients (Pickren et al. 1951).

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Not much research has been done into the immune histochemistry or cell structure of Ledderhose tissues (Allen et al. 1955), instead it is generally assumed to be the same as Dupuytren tissues. Very few clinical trials or studies into different treatments have been done so far, mostly investigating radiotherapy (Atassi et al. 2003; Heyd et al. 2010; Seegenschmiedt et al. 2012) or surgery (Wapner et al. 1995; Sammarco and Mangone 2000; Beckmann et al. 2004; Van der Veer et al. 2008) or the combination of both (de Bree et al. 2004).

Ledderhose Disease can be pain-free, but especially as the fibromas get larger, many patients experience a considerable amount of pain standing and walking on the affected foot. There is little information about prevalence available, but it is classed a rare disease by the Office of Rare Disease of the American National Institute of Health (ORD of the NIH), meaning it affects less than 200,000 people in the USA.

The aim of this survey was to assess the patients' experiences of the available treatment options and counselling, risk factors of Ledderhose Disease (LD), the relationship between LD and other conditions and needs of Ledderhose patients in general. This survey was part of an international survey that also addressed patients suffering from Dupuytren Disease described in part 1 of this book (Wach and Manley 2016).

49.2 Survey

49.2.1 Overview of the Survey

The international patient survey is described in part 1 of this book (Wach and Manley 2016). Patients with Ledderhose Disease (LD) and/or Dupuytren Disease (DD) were asked to fill out an online questionnaire. Patients were invited to participate via websites, forums and mailing lists by the supporting organizations (Wach and Manley 2016).

Overall the survey addressed for Ledderhose Disease:

- Quality of treatments
- Quality of counselling
- Family history
- Effect of lifestyle (smoking, drinking)
- Related diseases
- Needs of patients (open ended questions)

Patients were asked whether they are suffering from Ledderhose Disease, without requiring details about their diagnosis, although nodules in the foot can have a wide variety of causes (Macdonald et al. 2007). The survey did not specifically distinguish between nodules that have the same root cause as Dupuytren Disease and similar ones, maybe, for example, due to trauma (Gross 1957).

49.2.2 Surveyed Treatment Options

Treatments for plantar fibromatosis are in part different to those for Dupuytren Disease and have the aim of keeping the patient comfortable and mobile. In our LD survey, we inquire specifically:

- *Orthotics*: Insoles either just with padding under the foot or with a cut-out area to reduce the pressure on the fibroma when baring weight.
- *Steroicd injection*: Intralesional injections with anti-inflammatory effect, aiming at reduction of nodule size and pain relief.
- *Verapamil gel*: Applied topically for 6–12 months to reduce nodule size.
- *Cryosurgery*: Freezing the lump under a nerve block (Spilken 2012).
- *Shockwaves*: High-energy focussed extracorporeal shockwaves intending to soften the nodules and reduce pain as tested in a small study (Knobloch and Vogt 2012).
- *Collagenase injection*: Occasionally CCH (collagenase *Clostridium histolyticum*) injections into LD nodules are used off-label to soften the nodule.
- *Surgery*: Traditionally the treatment offered to most patients where conservative treatment is ineffective. The types of surgery used are local

excision, partial fasciectomy or (sub)total fasciectomy for patients with recurrence or more than one fibroma in the same foot (Beckmann et al. 2004). Recurrence after surgery, defined as re-appearance of nodules in the operated area, is frequent (25–75 %) and early, 'all within 14 months of surgery' (Aluisio et al. 1996).

- *Radiotherapy* (RT): Is still controversial in some countries, mainly because of the feared potential long-term risks and reluctance to treat a benign condition with RT. However, there is growing demand for it from patients as it has the ability to shrink the fibroma(s), reduce pain and allow return to normal life and even sport.

49.3 Results

49.3.1 Participating Patients

To achieve maximal participation, the responses for Ledderhose Disease were re-extracted in December 2015. Patient responses were mainly from Europe and the USA, with Canada and Australia contributing larger numbers of responses. Within Europe, the largest contributions were from the UK and Germany. After eliminating double entries, a total of 1000 Ledderhose patients responded (Table 49.1), 456 men with an average age of 53.8 and 544 women with an average age of 56.2.

Data correction was performed as described in part 1 (Wach and Manley 2016). Note that patients did not have to answer all questions; therefore, for any question the number of responses might be less than the total number of participants.

49.3.2 Age of Onset for Ledderhose Disease

The effect of gender, positive family history and having other (related) fibromatoses on the age of onset of Ledderhose Disease was evaluated. 888 patients specified their age of onset for LD, with an average age of onset of 44.6.

Table 49.1 Participants with Ledderhose Disease by country

Country	*N*	Country	*N*
USA	471	UK	163
Canada	46	Ireland	10
Australia	36	France	7
Germany	190	Other Europe	26
Holland	14	Africa	8
Austria	11	Rest of the world	18

49.3.2.1 Influence of Gender

Figure 49.1 shows that men develop Ledderhose Disease earlier than women. The average age of onset found for men is 41.4 (median = 43) and for women 47.5 (median = 50).

49.3.2.2 Family History and Concurrent Dupuytren Disease

Having a family history means that close relatives have or had Dupuytren and/or Ledderhose Disease. 528 patients reported having family history, 214 stated that they don't know ('unknown') and 251 had no family history or were not aware of any relatives with DD or LD. Below we are counting 'unknown' and 'no' as having no (known) family history. Patients with family history have an average age of onset of 43.3 and without family history an average age of onset of 46. Note that these are not prevalence data, i.e. having a family history might well mean that the chances to develop LD (or DD) are much higher, but the average age of onset is only a few years earlier.

78.2 % of the LD patients report suffering also from Dupuytren Disease. Overall, concurrent DD does not seem to have strong effect: the average age of onset for patients also suffering from DD is 45.4, even a little but not significantly later than the total average of 44.6. A strong difference appears when it is additionally taken into account which disease started first: patients with concurrent DD who had Ledderhose first report an onset of LD at 38, and if DD came first, the onset of LD was at 49.4. That difference is to some extent 'natural' because those with an early onset of Ledderhose Disease are all in the group

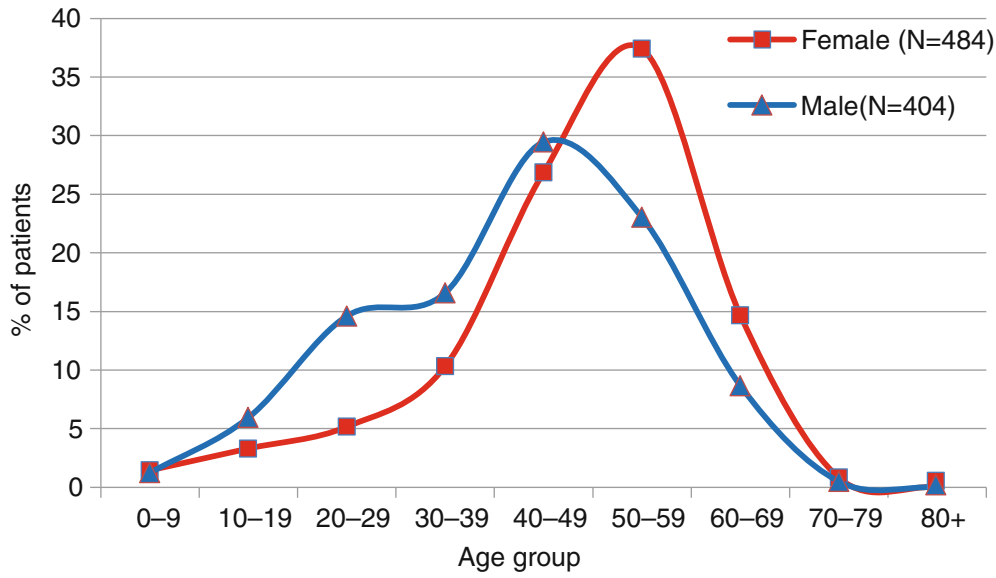

Fig. 49.1 Influence of gender on the age of onset of Ledderhose Disease

'Ledderhose first', thus lowering the average age of onset. If patients with an onset of LD <30 are excluded from the analysis, the average age of onset for the group with 'Ledderhose first' jumps to 46.8, while for 'Dupuytren first', the age of onset for LD increases only slightly to 51.

49.3.2.3 Lifestyle: Smoking and Drinking

Smoking is affecting the onset of Ledderhose Disease as shown in Fig. 49.2. For comparison also included in Fig. 49.2 are results for not smoking women without family history thus eliminating influences that might cause an earlier onset.

We found an average age of onset of Ledderhose Disease for smokers 40.2 (median = 40), for nonsmokers 45.0 (median = 48) and for nonsmoking women without family history 49.6 (median = 52).

For alcohol consumption, we observed no significant effect on the age of onset of LD. The average was 44.7 if drinking more than 2 glasses of wine/pints of beer per day, 44.2 if drinking less than 2 glasses of wine/pints of beer per day and 45.2 if not drinking at all. Our survey did not inquire about specifically heavy alcohol consumption.

49.3.3 Related Diseases

Of the patients with Ledderhose Disease, 78 % also have Dupuytren Disease, 22 % have or had frozen shoulder (of the DD patients 18 % have or had frozen shoulder), 26 % had knuckle pads (DD patients: 15 %), 16 % had thyroid problems (DD patients: 12 %), 5 % had diabetes (same as for DD patients), 1.3 % had epilepsy and 1.4 % had liver problems. 7 % of the male respondents have or had Peyronie disease (DD patients: 9.5 %).

For diseases with more than 50 respondents affected, we tested whether this co-morbidity is affecting the age of onset of Ledderhose Disease (average age of onset for all patients = 44.6, median = 47). We did not find a significant effect, except maybe for knuckle pads (Table 49.2).

49.3.4 Patients' Rating of Medical Counselling

Patients were asked 'Given your experience to date, how would you rank the medical community's knowledge and experience with Ledderhose

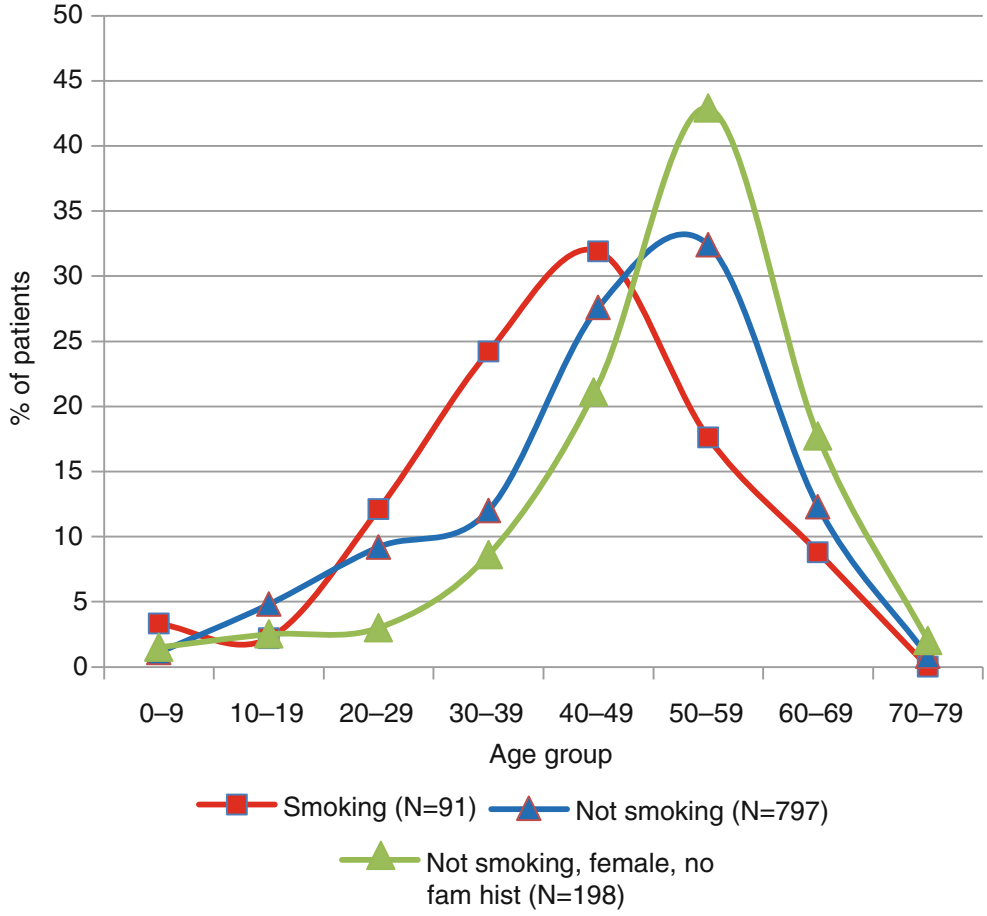

Fig. 49.2 Influence of smoking on the age of onset of Ledderhose Disease

Disease?' on a range of 1–10 with 1 = no knowledge and 10 = knew everything. Figure 49.3 shows results by country, whereby countries with less than 100 respondents are omitted. For better overview, the ratings 1–3 (= bad; red), 4–7 (= medium; yellow) and 8–10 (= good; green) are combined.

The ratings in all three countries are very similar, with Germany scoring only slightly better. When asked more specifically about the doctor's knowledge of the condition, various treatment options and associated conditions, the knowledge of the condition showed16% good ratings, but information about various treatment options and associated conditions achieved only 5–7 % good ratings (about the same for all 3 countries).

49.3.5 Patients' Rating of Treatments for Ledderhose Disease

Patients were asked to rate the effect of the treatments they had, using a score from 1 and 10, with 1 being the worst possible outcome and 10 being the best possible. For analysis, the 1–3 ratings, 4–7 and 8–10 have been combined (Fig. 49.4).

Patients who responded to the survey were most impressed with the result of radiotherapy. Cryotherapy comes out as second favourite, but the total number patients is small ($N = 15$). The 'classical' treatments surgery, orthotics and steroid injections all seem to be less effective than patients would like. Not included in Fig. 49.4 are 4 LD patients who reported injection of collagenase as

Table 49.2 Age of onset of LD for various co-morbidities

Co-morbidity	Frozen shoulder	Knuckle pads	Thyroid	Diabetes	DD = yes	DD = No	Peyronie
Ave. onset	45.7	39.4	48.4	44.3	45.4	41.7	44.8
Median	49	41.5	50	45	48	44	47
N	220	256	158	53	782	218	71

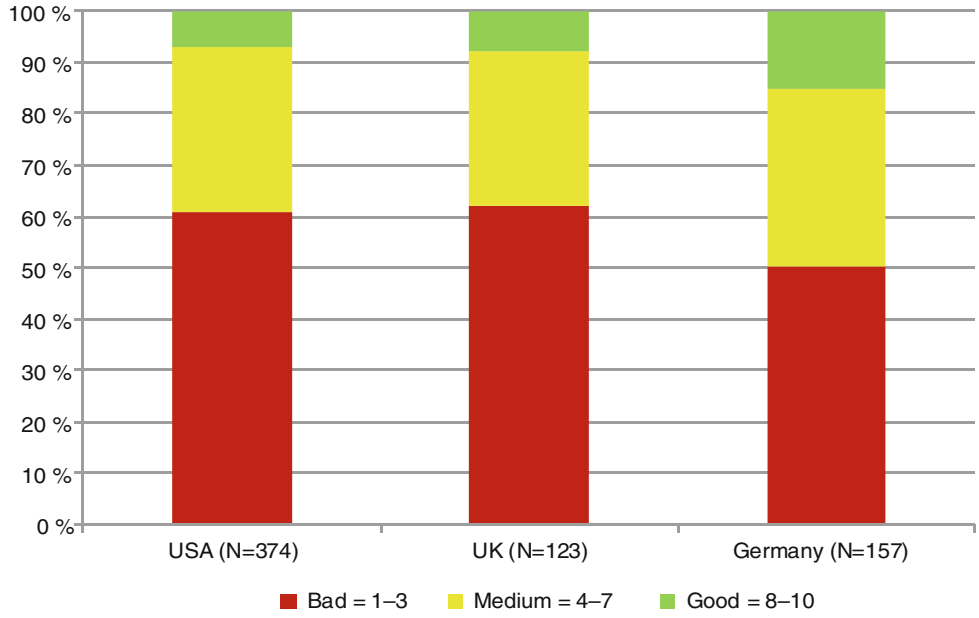

Fig. 49.3 Patients' rating of the medical counselling for Ledderhose Disease

an off-label use but were not impressed by the outcome (75 % bad, 25 % medium ratings). The ratings from patients who decided to have no treatment at all are included for comparison.

Patients could also indicate that they had 'other treatments' and many commented on those. This evidence is only anecdotal; no treatment was frequently mentioned in this category. Positively rated therapies were massaging (twice), tissue plasminogen activator (twice), Nexavar, proteolytic enzyme therapy, laser + verapamil, serrapeptase and topical iodine (each once).

49.3.6 Comments and Suggestions by Patients

At the end of the survey, patients were asked what they would wish from scientists and doctors and if they had any other remarks. Unsurprisingly many patients would like a cure, or failing that a lasting treatment that leaves them without pain. Better knowledge of disease and treatment options was requested by many patients, especially for general practitioners. Also suggested was earlier referral or treatment, not waiting until the condition causes real problems. Doctors should take family history into account, as patients with a strong family history have seen the devastating effects that Ledderhose and Dupuytren Disease can have.

More research was requested many times; patients appear unaware of what research is being done. Patients are also interested in alternative treatments, diet changes and possible anti-inflammatory or immune regulatory options to treat the condition. Many patients would like to see one doctor for all fibromatoses and regular

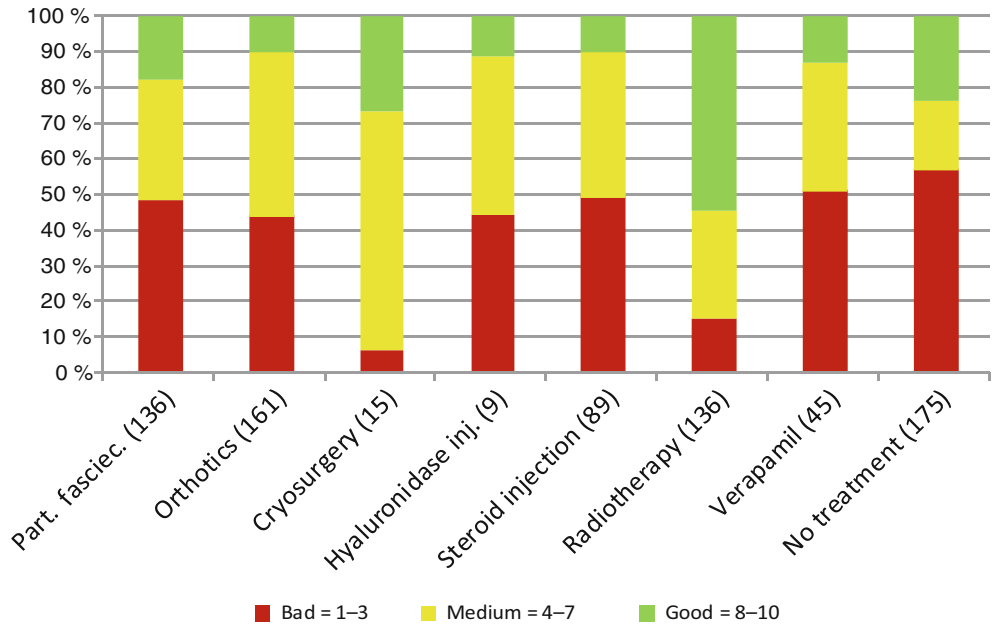

Fig. 49.4 Patients' rating of treatments for Ledderhose Disease

checks for patients once they have been diagnosed with one of the conditions. Last but not the least, stop thinking of Ledderhose (or Dupuytren) as a pain-free disease of alcoholics; neither statement is true.

49.4 Discussion

The goal of this survey was to assess the quality of counselling and treatments as perceived by patients. Additionally, the influence of potential risk factors should be explored. This was achieved by interviewing patients via an anonymous online survey. 1000 patients with Ledderhose Disease responded making this survey the biggest survey of LD patients so far.

49.4.1 Risk Factors

As patients were not selected for the survey on a statistical basis but were invited via mailing lists and websites, our survey is not suitable for providing reliable epidemiologic data. The World Health Organization states 'although plantar lesions arise more commonly in men, the gender difference is not as great as that found in palmar lesions' (Goldblum and Fletcher 2002). This might explain why we had more men than women in the Dupuytren group (ratio 1.4) (Wach and Manley 2016) but less in the Ledderhose group (ratio 0.84).

While we cannot judge whether a specific influence like smoking or family history makes it more likely to develop Ledderhose Disease, we can evaluate the age of onset of LD. We find an average age of onset of 41.4 (men) and 47.5 (women), respectively, similar to DD where the averages are 46 (men) and 50.1 (women) (Wach and Manley 2016). Male patients develop Ledderhose Disease earlier, and also smoking and family history result in an earlier onset, while we found no effect of moderate drinking.

We did not observe a strong influence of comorbidities, maybe with the exception of knuckle pads. The connection with Dupuytren Disease is strong: 78 % of the LD patients also suffered from DD. But suffering from DD did not strongly affect the age of onset (Table 49.2). There is a possibility that we are surveying two types of Ledderhose Disease: the one type could be the

aggressive form that makes Ledderhose Disease start early, e.g. onset in Fig. 49.2 at the age at 35 or earlier. The other group could be patients developing Dupuytren Disease first. Those will likely become sensitized by DD and observe their feet more thoroughly. They might find nodules that they would have never noticed without having DD. We suspect that this group might have a larger contribution of light LD with later onset. This is supported when looking at the severity of Ledderhose Disease (scale 1–10 with 1 = least severe). The average severity of Ledderhose Disease if LD developed first was 4.9, while for those who developed DD first, the average severity was 3.7.

Based on this observation, we recalculated the age of onset for those who developed Ledderhose Disease *first*. If those patients did not develop DD, the age of onset of LD was 39.3. If they did develop DD, the age of onset of LD was slightly earlier, at 38. We conclude that developing both diseases is possibly an indication for a more aggressive disease, but the effect on the age of onset of LD seems small.

49.4.2 Quality of Counselling and Therapies

One of the most striking results of this survey is the perceived low quality of medical counselling. Patients are obviously very dissatisfied with the advice they received. In the medical community, a broader awareness of all therapeutical options and of related diseases would be very helpful for improving consultations.

Most of the surveyed treatments received bad rating in the 45–50 % range and just 10–20 % good ratings. Only radiotherapy with 54 % good ratings and cryosurgery with 18 % (and only 7 % bad ratings) seem to offer better chances for success in treating Ledderhose Disease. Unfortunately for patients, these two treatments are lacking availability: radiotherapy is available in Germany, to some extent in the USA and very limited in the UK and a few other countries. Cryosurgery for LD seems to be available only in the USA, at least according to our survey. The treatment situation of LD could thus be much improved by better availability of these two treatments and possibly by new effective treatments.

49.4.3 Potential Biases and Errors

For our survey, there is a variety of potential biases and errors. This includes that inviting patients via forums and mailing lists might create a bias towards dissatisfied patients because those might be the ones more likely checking the Internet for information. Further, in an Internet survey, typically the elder patients are underrepresented. As indicated in the discussion of the Dupuytren part of this survey (Wach and Manley 2016) an online, not assisted self-reporting (instead of medical records) may be subject to misunderstandings, entry errors and recall errors. Nevertheless, we believe that the ratings of medical counselling and treatments are based on a sufficiently high number of answers and are clear enough to indicate actual facts.

Conclusions

This survey should be seen as a guide towards patients' backgrounds, ideas and treatment preferences and can be helpful to doctors to better understand the relationship between Ledderhose and other conditions and what patients want from a doctor. The survey exhibited:

- The quality of medical counselling for Ledderhose Disease can be improved considerably.
- The typical LD treatments, orthotics, steroid injection and surgery seem to have only limited benefit and bad results in about 50 % of cases.
- Radiotherapy and cryosurgery are perceived by patients as the relatively best treatments but have limited availability in most countries.
- Male gender, family history and smoking seem to cause an earlier onset of Ledderhose Disease. We did not find an effect of moderate alcohol consumption on the age of onset.

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Peyronie Disease

50

Mels van Driel

Contents

50.1 Introduction

Peyronie disease (PD) is a localized connective tissue disorder characterized by changes in the collagen composition that results in abnormal deposition of fibrous tissue in the tunica albuginea of the penis, causing a penile deformity and a subsequent degree of erectile dysfunction (ED). The area of inelastic scar tissue, named *plaque*, restricts expansion of the involved part of the penis, causing the erection to curve. Although its etiology has not been elucidated, PD probably results from the presence of a predisposing genetic susceptibility combined with an inciting event, most probably microtrauma. PD appears to be more common in northern European Caucasians; it is uncommon in African-American men and very rare in Asians (Sommer et al. 2002).

Globally, the incidence of PD appears to be increasing. This may be due to the availability of oral pharmacotherapy for men with ED, who would otherwise have been unaware they had a penile curvature. In addition, there is a greater awareness of male sexual dysfunctions due to broad media coverage as well as the acceptance that conditions as PD can be openly discussed and brought to the attention of physicians without embarrassment.

50.2 Historical Background

François Gigot de la Peyronie (1678–1747) was a French surgeon who was born in Montpellier, France. As a teenager, he studied philosophy and surgery in Montpellier, where in 1695 he received his diploma as a barber-surgeon. He continued his education in Paris as a student of Georges

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Mareschal who was chief-surgeon at the Hôpital de la Charité. In 1736, after the death of Mareschal, he became first surgeon to King Louis XV. He took interest in the medical educational system, reorganized surgical schools, and played a major role in the creation of a 1743 law that banned barbers from practicing surgery.

De la Peyronie (1678–1747) was the first to provide a comprehensive description of the symptoms of *induratio penis plastica*, the name in the German scientific literature (De la Peyronie 1743). PD had been anecdotally described for centuries as an obscure obstacle to marital bliss and repeatedly discussed in treatises by famous authors like Theodoric of Bologna (1265), Wilhelm of Salieto (1275), Gabriele Falopio (1561), Andres Vesalius (1543), Julius Caesar Arantius (1579), and Nicolaes Tulp (1641) (Hauck et al. 2005).

De la Peyronie thought he was dealing with a sexually transmitted disease. He described the plaques as painless knots that among elderly men could be palpated along the corpora cavernosa singly or in rosary-like formations, and he observed that the curvature was always on the same side as the plaque. His remedy of choice was a cure with holy water of the Barèges thermal spring in the French Pyrenees. Other important names in the history of PD are summarized in Table 50.1. The first excision of a plaque was done in 1828 (Mc Clellan 1828) and the first excision combined with free fat grafting in 1943 (Lowsley 1943).

Table 50.1 Historical landmarks of Peyronie disease

1265 Observed by Theodoric of Bologna
1743 First full description by François de la Peyronie
1828 First surgical excision of a plaque by George McClellan
1943 Plaque excision and free fat grafting by Oswald Lowsley
1965 Nesbit procedure for congenital curvature by Reed Nesbit
1979 Nesbit procedure used for PD by John Pryor
1998 Plaque incision and venous grafting by Tom Lue

50.3 Pathophysiologic, Histopathologic, and Genetic Aspects

PD affects the tunica albuginea, producing areas of local fibrosis and loss of tissue compliance (Gelbard 1993). The normal tunica albuginea is composed of a lattice of collagen and elastic fibers arranged in two layers: an outer longitudinal one responsible for elongation during erection and an inner circular layer for increasing the width. The tunica is separated from the erectile tissue by a loose connective tissue sleeve containing a network of vascular and lymphatic tributaries. The venous drainage of the erectile tissue is via the emissary veins that transverse through the tunica and into the dorsal vein. The movement of the two tunical layers across each other during erection, thereby compressing these veins, is the main feature of the veno-occlusive mechanism of erection.

The most widely accepted theory is that the disease process is initiated by mechanical trauma to the tunica albuginea of the erect penis, resulting in aberrant wound healing and subsequent scar tissue formation. As the penis engorges with blood during erection, it expands its girth and extends its length until the tunica and the strands of the septum in between the corpora cavernosa are stretched to the limit of their elasticity. If the penis is forcefully bent during vigor intercourse, the attachments of the septal fibers to the tunica are stressed, generating tension. In young men the elasticity of the tissues will permit the structures to deform and rebound without damage. However, as a man ages, the tunica albuginea becomes less elastic, and the tension associated with the same degree of distortion can delaminate its circular inner fibers (Devine and Jordan 1994). This tear causes bleeding and clot formation, leading to the deposition of fibrin, fibroblast activation and proliferation, enhanced blood vessel permeability, and generation of inflammatory cells. The infiltrate consists of T-lymphocytes, macrophages, and plasma cells surrounding the small vessels in the subtunical layer. This infiltrate is followed by focal areas of fibrosis that eventually develop into plaques. This active process lasts for 12–18 months. Most but not all patients have pain associated with the inflammation present in the active phase.

Histological examination of excised plaques shows fibrin deposition within the plaques and dense collagenous connective tissue and calcification. Calcification can occur early after the onset of a plaque and is not, as previously thought, an indication of mature disease. The fibrosis in PD does not invade or replace the spongious tissue of the corpora. Some inflammatory changes can be seen in the space between the tunica albuginea and Buck's fascia, but fibrosis of Buck's fascia itself does not occur except in patients treated by intralesional injections or radiotherapy.

Genetic predisposition plays a role in PD. PD is associated with other fibrotic conditions such as Dupuytren Disease (DD) and Ledderhose Disease. We evaluated the coexistence of DD in 415 consecutive patients with PD and found DD in 22 % of them (Nugteren et al. 2011). Previous reports concerning coexisting DD in smaller series of patients presenting with PD show ranges varying from 0.01 to 58.8 %, a positive family history for PD in 1–4 %, and a positive family history for DD in 9.8 %. DD is thought to be the most common hereditary connective tissue disorder in Caucasians. However, the true prevalence rate of PD may be even higher than DD because PD is underreported.

One study that compared the gene expression profiles of patients with PD and DD noted similar alterations in the genes responsible for collagen deposition degradation, ossification, and myofibroblast differentiation (Qian et al. 2004). Dolmans et al. observed significant association of PD with single nucleotide polymorphisms (SNP) rs4730775 at the (WNT2) locus on chromosome 7 (Dolmans et al. 2012). WNT means "wingless-type MMTV integration site family." WNT2 is a member of this WNT gene family, which consists of structurally related genes that encode glycoproteins. These act as extracellular signaling factors. The best understood WNT signaling pathway is the canonical pathway, which activates the nuclear functions of b-catenin, leading to changes in gene expression that influence cell proliferation and survival (Moon et al. 2004). A recent study revealed increased levels of b-catenin, the end product of WNT signaling, in cells derived from plaque from PD patients compared with cells from normal tunica albuginea tissue (De Young et al. 2010). This suggests that the WNT signaling cascade is overstimulated in PD.

50.4 Clinical and Diagnostic Aspects

Patients with PD range in age from 20 to 80 years, with a median age of 53. PD prevalence rates range between 3 and 9 % of all adult men (Porst et al. 2012). PD presents in two distinctive phases, an inflammatory phase lasting 6–18 months with painful erections and the development of a penile curvature, followed by a chronic phase characterized by stable plaque formation and a variable degree of ED (Table 50.2). Patients are often anxious over real or imagined loss of sexual capacity and worry about the future course. Occasionally they think they have a tumor. The deformity is sometimes so severe that vaginal intromission becomes impossible. However, difficulties with penetration depend not only on the curvature but also on the anatomical condition and cooperation of the partner. A sexually active single man with marked deformity is likely to suffer more than a man within a stable and long-standing marital relationship.

PD can cause a great deal of functional and psychological distress to the patient and his partner. We insist that the partner accompanies the patient at an early visit, so that an explanation of PD can be given to both. Each patient is asked to bring or to send photographs of his erect penis to

Table 50.2 Characteristic features of the early and late phases of Peyronie disease

Early inflammatory phase	Late stable phase
Induration with or without fleshy tender plaques	Well-established plaques, can be nodular and with calcification
Progressive penile deformity	Nonprogressive deformity
Variable erectile dysfunction	Penile shortening
Pain on erection	Erectile dysfunction

monitor disease progression. A picture of his full erect penis from above will document lateral curvature, lateral pictures dorsal or ventral curvature, and a frontal view right, left, or a combined curvature as well as penile shaft rotation. A PDE5 inhibitor or an intracorporeal injection with a vasodilating drug may be used in patients who have concomitant ED. The curvature is best measured by goniometry.

Physical examination must be precise. The glans is grasped with one hand and the penis gently stretched to the limit. During this maneuver, it is possible to assess the overall elasticity of the penile shaft. A marked loss of elasticity denotes scarring in the longitudinal axis. The stretched penile length is measured from the urethral meatus to the level of the abdominal skin. This is important because penile shortening usually occurs already before surgical intervention. The edges of the plaque are palpated between the index finger and the thumb of the other hand (without a glove) placed laterally on the shaft. Dorsal plaques are the most common and can be differentiated easily from ventral plaques. Lateral plaques may produce significant deviation of the natural angle of coitus, making intercourse particularly problematic. Circumferential plaques will result in an hourglass deformity with distal flaccidity. Plaque locations should be noted, but precise size assessment by palpation is not reliable. Clinical signs of DD and Ledderhose nodules should also be checked.

Extensive investigations are not always required in the early stages of PD. However, today there is common agreement that color duplex ultrasound is a useful diagnostic tool in the majority of PD patients. Typical features include thickening of the tunica albuginea, calcifications, and septal fibrosis. PD patients with concomitant ED may have arterial or veno-occlusive dysfunction. For this reason, it is important to combine duplex ultrasound with an intracavernosal injection erection test. Magnetic resonance imaging (MRI) can provide detailed images of plaques, but it is time-consuming and expensive and is reserved for special cases. Before discussing any treatment modality, the patient and his partner should be informed about spontaneous regression rates between 3 and 13 % (Bekos et al. 2008). Since PD is significantly more frequent in diabetes and often associated with androgen deficiency, serum glucose and glycosylated hemoglobin (HbA1C) as well as total testosterone and SHBG or free testosterone should be considered as baseline lab assessments (Porst et al. 2012).

50.5 Nonsurgical Therapy

Pharmacotherapy options include oral pentoxifylline, potassium para-aminobenzoate (PABA), intralesional treatment with verapamil, clostridial collagenase or interferon, topical verapamil gel, and iontophoresis with verapamil and dexamethasone. These may be efficacious in some patients, but in the European guidelines, none of these options carry a grade A recommendation (Hatzimouratidis et al. 2012). Collagenase *Clostridium histolyticum* is currently the only drug approved by the Food and Drug Administration for intralesional injection in patients with a palpable plaque with dorsal or dorsolateral curvature >30°. Oral steroids, vitamin E, and tamoxifen should be avoided. Extracorporeal shock wave treatment and penile traction devices should only be used to treat penile pain and reduce penile deformity, respectively. Penile traction can be painful, and effectiveness is highly dependent on patient compliance. Radiation has been used for the empirical treatment of PD with mixed results throughout the literature (Mulhall et al. 2012). Low-dose RT in the early stages of PD seems to be effective in patients with painful erections not improving with time or with the use of oral or intralesional therapies. However, according to the European Society for Sexual Medicine, penile radiotherapy failed to show any convincing efficacy but bears a not well-defined risk of local complications and should therefore be considered outdated (Porst et al. 2012).

Overall success rates of nonsurgical treatments are difficult to interpret because of variations in study design, patient populations, treatment durations, and doses used, as well as

small sample size (Porst et al. 2012). A major limitation comparing study outcomes is inconsistent outcome endpoints. Reduction of erect penile deformity (curvature, narrowing, shortening) is the most critical outcome measure. Future trials for PD should have at least a three-arm study design (test treatment vs. placebo vs. no treatment) with study duration of 18 months.

50.6 Surgical Therapy

The aim of surgery is to correct the curvature and allow comfortable penetration. Surgery is indicated only for patients with stable disease and serious difficulties with sexual intercourse. Specific issues that should be mentioned during patient consent are the risks of erectile dysfunction, glans numbness due to dorsal nerve injury, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, the potential need for circumcision at the time of surgery, and penile shortening. It is imperative therefore that the stretched penile length is measured preoperatively so that the patients realize that the length loss postoperatively is mainly a result of the disease itself and not the surgery.

50.6.1 Nesbit Procedure and Other Shortening Techniques

In 1965, Nesbit was the first to describe elliptical tunica excision opposite a nonelastic corporal segment to treat congenital penile curvature (Nesbit 1965). Fourteen years later, this technique was reported for PD (Pryor and Fitzpatrick 1979). When the penis is not too short, the preferred technique of many surgeons is a Nesbit procedure (Fig. 50.1a–d) or other shortening techniques such as those described by Essed-Schröder, Yachia, and Lue. Advantages include short surgical time, no significant negative effect on erectile hemodynamics, good cosmetic outcomes, simplicity, safety, and effective straightening. Disadvantages are further shortening and the fact that an hourglass deformity or other complex curvatures cannot be corrected adequately with shortening techniques. My personal lower limit to recommend a Nesbit procedure is an erect penis of 12 cm measured at the longest (convex) aspect.

50.6.2 Plaque Incision/Excision with Grafting

In patients with extended calcifications, complex deformities such as an hourglass, or in those with a concave side length less than 11 cm, a lengthening procedure such as plaque incision or excision with grafting should be considered (Fig. 50.2a–d). Such procedures have 10 % risk of penile shortening. Prolonged sensory disturbances of the glans due to mobilization of the neurovascular bundle and the risk of ED (20–30 %) are the main disadvantages. Posttreatment ED is either due to inflammatory reaction and fibrosis beneath the graft, leading to corporeal smooth muscle damage or due to venous leakage. These techniques should not be used in patients who have suboptimal preoperative rigidity.

The most common autologous materials are the saphenous vein, dermis, buccal mucosa, rectus fascia, and fascia lata. The most common extracellular matrix graft materials are bovine and human cadaveric pericardium, porcine small intestinal mucosa, and cadaveric fascia lata.

50.6.3 Prosthesis Implantation

Men who suffer from both ED and PD do not always respond to PDE5 inhibitors or intracorporeal injections with a vasodilating drug. In such cases, a simple straightening operation does not provide any benefit, as insufficient rigidity still impedes intercourse. For these patients, surgical correction of the curvature should be performed with simultaneous hydraulic erection prosthesis implantation. In general, such an operation in combination with manual remodeling guarantees a straight penis with sufficient rigidity for sexual intercourse. However, despite extensive counseling, half of patients will be dissatisfied with the

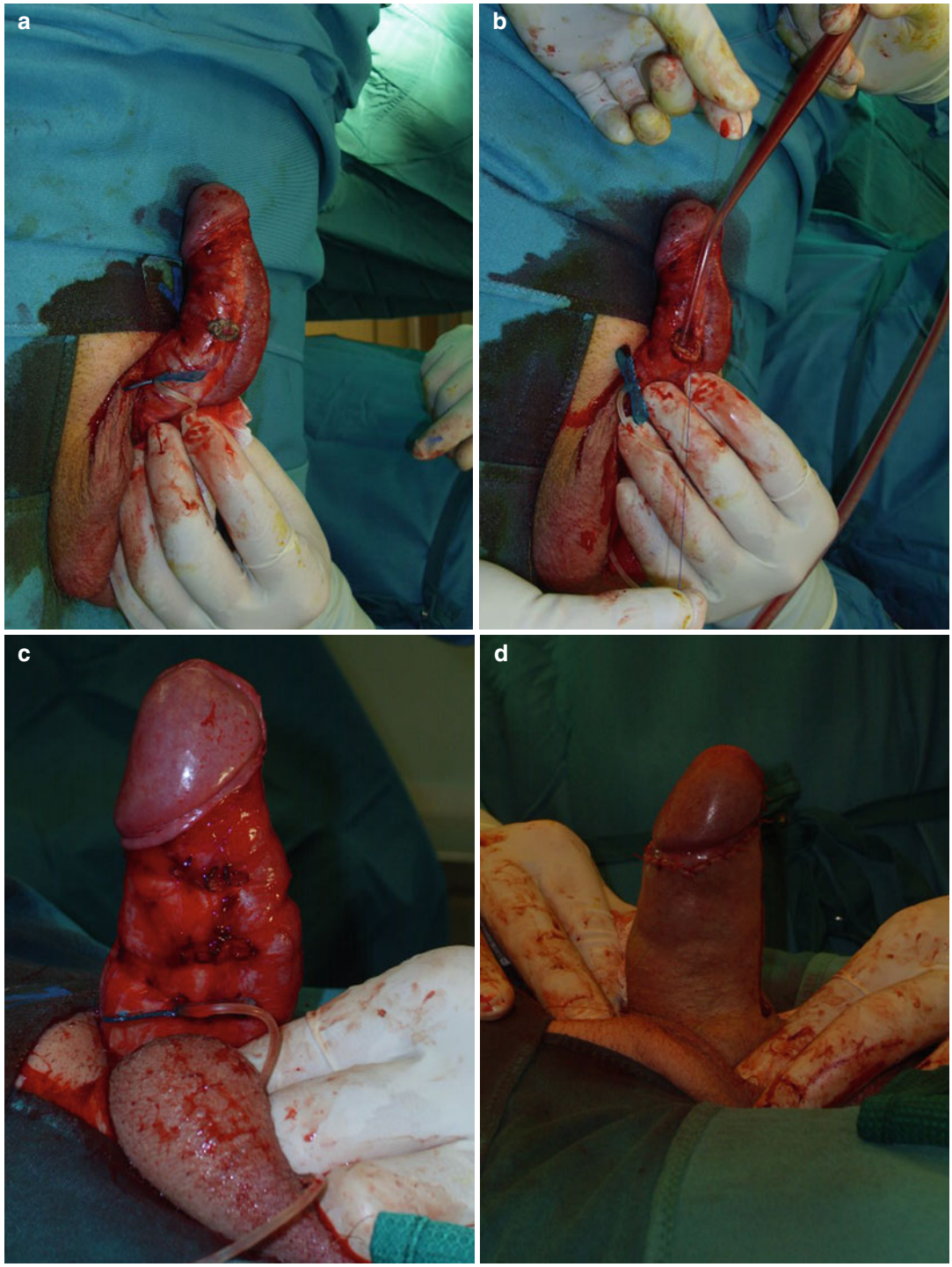

Fig. 50.1 (**a**–**d**) Nesbit procedure. (**a**) Degloved penis after circumcision; artificial erection with saline with marked ellipse of tunica. (**b**) Tunical ellipse has been excised. (**c**) The defects stitched with Vicryl. (**d**) Straight artificial erection at the end of the procedure

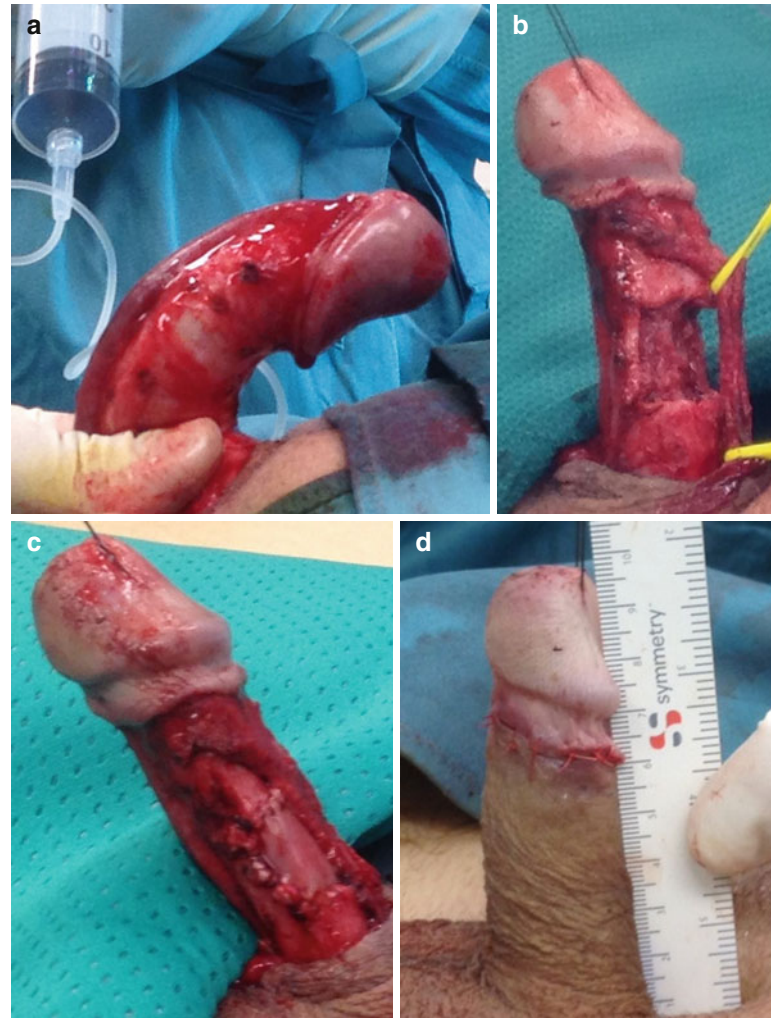

Fig. 50.2 Plaque incision and grafting with bovine pericardium. (**a**) Degloved penis after circumcision; artificial erection with saline. (**b**) Tunical defect after plaque incision and trimming of sharp edges, isolated neurovascular bundle. (**c**) After grafting with bovine pericardium, the neurovascular bundle still lays aside. (**d**) After closure in layers

postoperative penile length. In this group, a simultaneous penile lengthening procedure should be considered.

50.7 Discussion

PD is a well-defined clinical entity comprising penile fibrotic alterations with penile deformity and shortening, often associated with sexual dysfunction. This disease can affect the sexual confidence of men. Counseling is very important. Many oral medications are available for the management of the acute phase of PD, but evidence for their use is weak. Intralesional collagenase *Clostridium histolyticum* is the only currently FDA-approved drug for the management of PD. Its indications are, however, limited to patients with palpable plaque with dorsal or dorsolateral curvature >30°. Traction therapy, as part of a multimodal approach, is possibly an underused additional tool for the prevention of PD-associated loss of penile length, but its efficacy is highly dependent on patient compliance.

A man should only be considered as a candidate for surgical correction if he and his partner experience problems with sexual intercourse and he has PD for at least 12 months with no change in deformity for at least 3 months. As the patients' expectations are frequently unrealistic, preoperative counseling is paramount for acceptable satisfaction rates (Reisman and Cruz 2013). Patients

must be aware that the aim of surgery is to make the penis functionally straight, which is defined as a curvature of less than 10–20° and that some degree of penile shortening will nearly always be a potential complication.

Bullet Points

- The precise cause of Peyronie disease is not yet known.
- Evidence suggests that biomaterial failure of the tunica albuginea in the genetically predisposed individual plays an important role in the pathogenesis.
- Nonsurgical therapies have rather disappointing outcomes (missing radiotherapy).
- The majority of Peyronie disease patients do not require surgery.
- For those who need surgery, careful preoperative assessment, counseling, and consent must be followed by meticulous surgical technique bases on understanding of the role of the tunica albuginea.

Conflict of Interest Declaration The author is a speaker for GlaxoSmithKline and Lilly.

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Part X

Future Paths of Research

Charles Eaton, Marie Badalamente, and David O'Gorman, supported by Paul Werker and Bert Reichert

The Next Stage of Clinical Dupuytren Research: Biomarkers and Chronic Disease Research Tools

51

Charles Eaton

Contents

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51.1 Introduction

Dupuytren Disease is a common problem. Surgeons have been working for almost 200 years to develop better treatment options. Despite this, long-term outcomes have been stagnant for decades because the focus has been on management of local complications of disease. Further progress requires shifting the goal from treating hand contracture to finding and treating the systemic basis of disease.

51.2 What Are Unresolved Issues with Current Approaches to Dupuytren Clinical Research?

51.2.1 Dupuytren Contracture Procedure Long-Term Effectiveness May Have Reached a Plateau

The history of Dupuytren treatment reflects the pursuit of two conflicting goals. The first goal, longer disease remission, pulled surgeons from less invasive to more invasive treatment, from fasciotomy to fasciectomy to radical fasciectomy to dermofasciectomy. The second goal, lower treatment morbidity, pushed surgeons back toward less invasive treatment. The result has been chronic controversy and oscillation in popularity of different options but, over the long term, change without progress. Patients still bear the burden of choosing risk versus recurrence for a benign disease. Lost in the drama is the fact that we may be close to the *theoretic limit of the effectiveness of disease management by a single local treatment*. The rate of progression of untreated Dupuytren Disease from nodule to deformity impairing function is about 2% per year (Gudmundsson et al. 2001; Reilly et al. 2005), which is about the same as the lowest reported recurrence rates after extensive dermofasciectomy (Abe et al. 2007; Searle and Logan 1992; Ketchum and Hixson 1987; Armstrong et al. 2000; Villani et al. 2009). However, this is not the end of the road. Several centers are currently developing protocols to assess multimodal treatment effectiveness, such as combining minimally invasive contracture release with single-dose radiotherapy or testing the role of adjuvant pharmacotherapy with fasciectomy.

51.2.2 Dupuytren Treatment Algorithms Have Changed Little Despite the Introduction of New Procedures

Despite public fanfare and social media fueling patient interest in new options, most patients are offered a limited set of procedures (Fig. 51.1) and

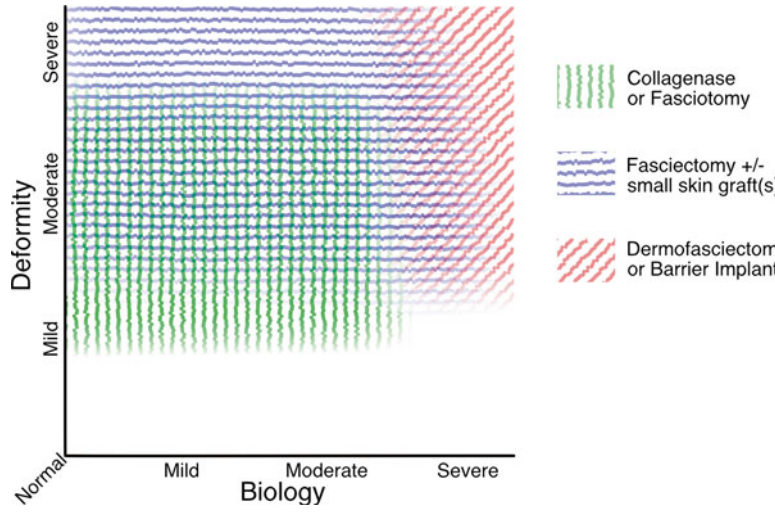

Fig. 51.1 Current procedure options for Dupuytren contracture. Recommendations are based on the physician's qualitative assessment of both the severity of contracture and the biologic severity of disease. This shows the considerable overlap in choices of treatment for most stages of contracture

follow a clinical path that has changed little in the last 50 years (Fig. 51.2). There are several reasons for this. The first is that *physicians treat the contracture but not the disease which caused it*. The visibility and drama of the deformity diverts attention from the fact that contracture is only a complication of the larger problem of Dupuytren Disease. The second reason is that because there has never been a widely accepted effective medical treatment for Dupuytren Disease, both treatment and disease research are deferred entirely to surgeons, who *focus on technique-oriented research*. The third is *inertia*. Because of resistance of surgeons to endorse radiotherapy and lack of an effective pharmacologic option, most physicians tell patients that their only options are either a procedure or nothing. There is one exception to this situation. Collagenase protocols, documenting effectiveness of treating contractures of 20°, have shifted the treatment algorithm of minimally invasive procedures to treat contractures of less severity than had been common. This expansion of indication reflects the lower morbidity of minimally invasive treatment. It's tempting to speculate that minimally invasive intervention and re-treatment for lesser degrees of contracture will prevent secondary tendon and joint changes, leading to better overall long-term results. Time will tell.

51.2.3 The Natural History of Untreated Dupuytren Disease Is Virtually Unknown

Current Dupuytren triage and treatment result in a potentially large percentage of undocumented patients. Many patients avoid surgical consultation because of rumor, family, or personal experiences with Dupuytren treatment morbidity. Many patients are diagnosed and told not to return until they have developed severe deformity. Many patients change surgeons after consult or treatment, hoping for a better outcome, and are lost to follow-up. Without a biomarker, the variability of disease progression and the lack of data on untreated disease mean that it is impossible for studies of prophylactic treatment to provide statistically meaningful outcome data, even when hundreds of patients are involved.

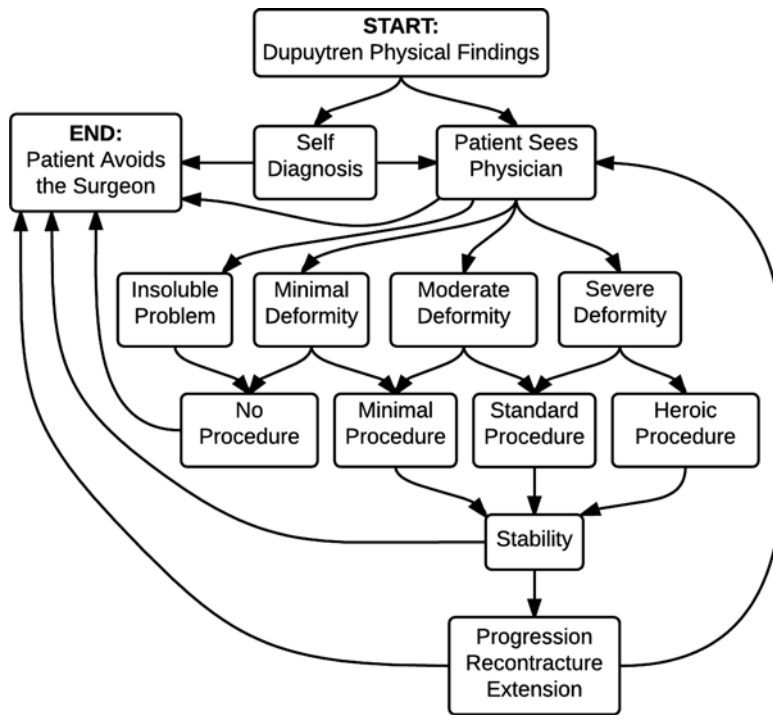

Fig. 51.2 Map of common routes of Dupuytren triage and treatment. This map of treatment paths remains unchanged despite changes in procedures for Dupuytren contracture. In this surgical disease model, treatment may reach an end point for reasons other than cure

51.2.4 Retrospective Health Record Reviews Lack Essential Dupuytren Data

Only 1 out of 7 patients with Dupuytren Disease can be expected to have the diagnosis documented in their medical records (DiBenedetti et al. 2011a). Dupuytren-specific information such as age of onset, family history of Dupuytren Disease, and Dupuytren Disease-specific quality of life assessment is only documented in patients being evaluated for treatment by surgeons and inconsistently even in this subgroup. Without a Dupuytren-specific survey, simple record review cannot extract details of dynamic relationships such as the timing of Ledderhose appearance, timing of medication use, or other medical events to the individual time line of Dupuytren appearance and progression.

51.2.5 Clinical Dupuytren Research Models Lack Statistical Power to Address the Simultaneous Unknowns of the Dupuytren Biology

Clinical research is daunting because many variables dynamically influence Dupuytren activity (Fig. 51.3). Dupuytren Disease often has a slow or intermittent progression to the complication of deformity. Dupuytren contracture has great individual variability of presentation and may be confounded by development of secondary pathoanatomy of joints and tendons. We still lack standard assessment of severity or standard definitions of outcome. There are wide variations in treatment technique within each type of procedure. There are wide variations of biologic

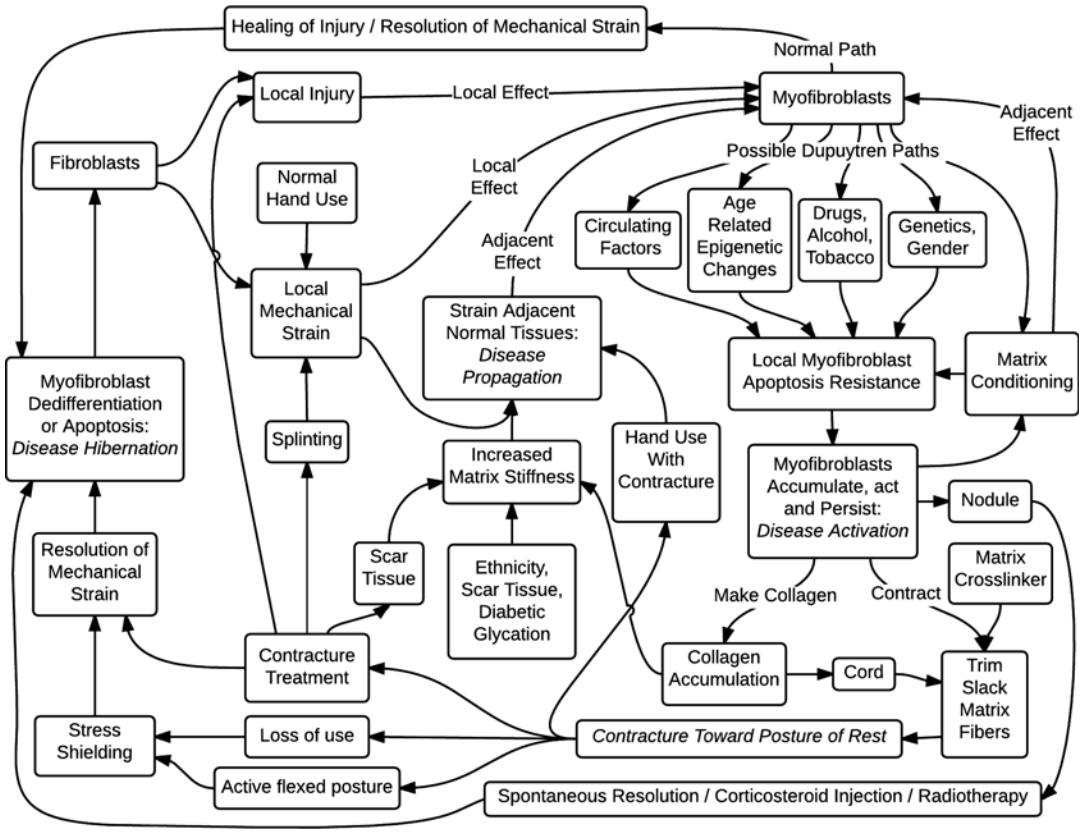

Fig. 51.3 The complexity of Dupuytren influences. Dupuytren biology is dynamically influenced by many interconnected factors. This diagram is a simplification, and every box on this diagram is, in turn, a simplification of an entire field of investigation and publications

aggressiveness of patients treated with the same procedure. Finally, the facts that early Dupuytren Disease is not documented in the majority of cases (DiBenedetti et al. 2011a) and that the USA lacks a centralized medical database pose large obstacles to the study of the natural history of disease.

51.2.6 Progress Requires Exploration of Different Research Models and Goals

We've been using the wrong tools and aiming at the wrong target to change long-term outcomes. Dupuytren contracture is the crime scene, not the criminal. Our goal should be prevention, not salvage. We must move the focus to disease before deformity. This requires a shift of Dupuytren research from surgical disease research models to chronic disease research models (Table 51.1). Dupuytren Disease is a chronic systemic disorder with episodes of contracture activity. Dupuytren *contracture* is in some ways the least important and least informative aspect of Dupuytren *Disease. Surgical research* has several distinct features. It is generally organized in a top-down fashion with a set duration and end point. Surgical research usually focuses on anatomy and technique. It often uses procedure-oriented metrics to assess specific outcome metrics over a short-term fixed duration of study. It answers questions such as "how much was the immediate improvement?" or "what complications occurred?" when comparing different procedures or different study groups undergoing the same procedure. Surgical research represents the majority of Dupuytren research publications and provides valuable guidance to refine technical approaches to contracture management. It has done little toward the development of a cure for Dupuytren Disease. *Chronic disease research* is often structured for exploration rather than refinement. Chronic diseases, by definition, are chronic because they lack effective long-term treatment. Lack of treatment often stems from lack of understanding of disease biology. Chronic disease research begins by surveying the variety and impact of disease to formulate a clinical disease description. This description guides the search for what questions to ask to identify the cause of disease. Chronic disease research is patient guided, focusing on quality of life metrics, identifying subsets of disease severity, and using biomarkers to guide individualized treatment of different disease subsets. It is typically longitudinal, long term, and open ended. *This approach has not been previously applied to large-scale Dupuytren research.*

51.3 Biomarkers Are Essential for Research to Answer Many Questions About Dupuytren Disease

51.3.1 What Is the Definition of Dupuytren Disease?

The diagnosis is usually made retrospectively, after the patient has already developed the

Table 51.1 Differences between surgical disease and chronic disease clinical research models

Research model	Disease types	Research goals	Design
Surgical disease	Acute Stable post-event Anatomic origin Affect function	Refine treatment Define anatomy Compare techniques Local biology	Top-down Procedure centric Short term End point
Chronic disease	Chronic progressive Biologic origin Affect quality of life Affect mortality	Find the cause Define natural history Find biomarkers Find molecular targets	Survey based Patient centric Long term Open ended

Surgical disease research and chronic disease research are applicable to different disease scenarios. They employ different overall design structures because they have different goals. Further progress in Dupuytren care may be possible by studying the condition as a chronic disease

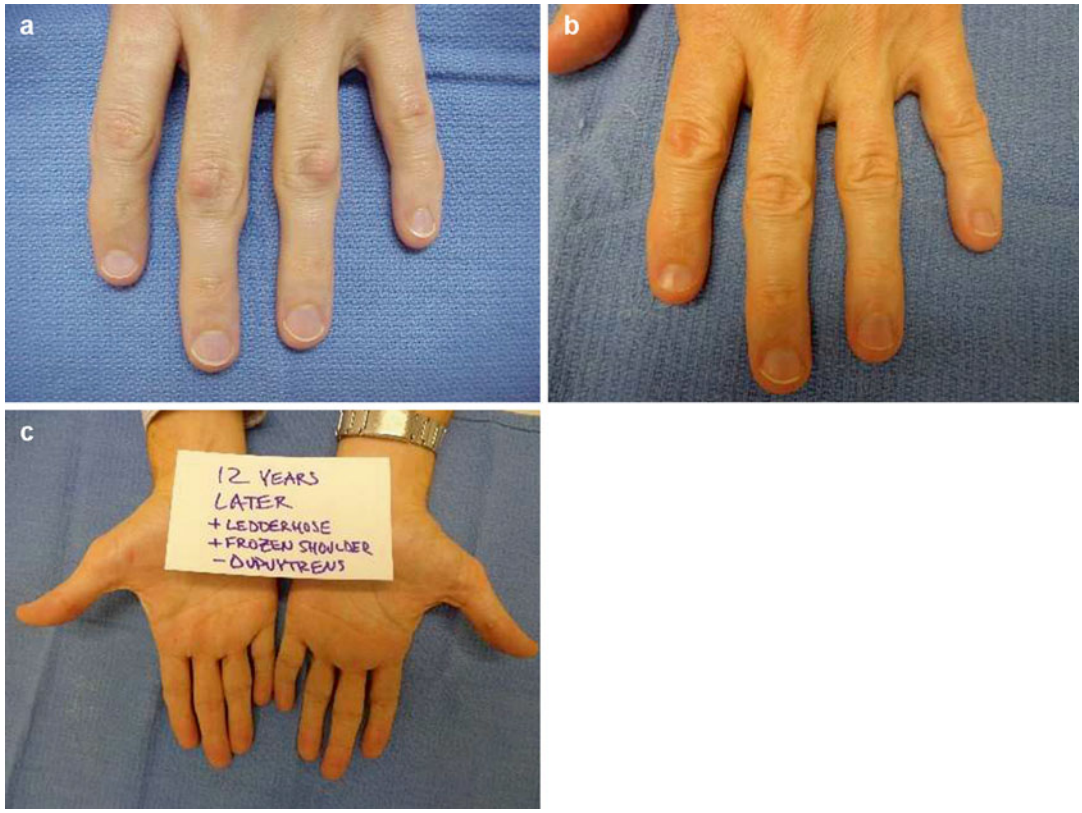

Fig. 51.4 Is this Dupuytren Disease? (**a**) This patient presented with typical Garrod knuckle pads involving the proximal interphalangeal joints of the left middle and ring fingers, but no palmar disease. (**b**–**c**) Follow-up 12 years later. During the following 12 years, the patient had no hand treatment. The original Garrod pads spontaneously resolved, but a new Garrod pad developed on the left index finger. In this time, the patient developed Ledderhose Disease and had an episode of frozen shoulder, but still has no evidence of palmar disease

complication of Dupuytren contracture affecting the palms. Aggressive Dupuytren Disease appears elsewhere as Garrod knuckle pads, Ledderhose, and frozen shoulder. Are these conditions simply part of Dupuytren Disease? If these conditions are present despite unaffected palms (Fig. 51.4), is this still considered Dupuytren Disease? *This question cannot be answered without a laboratory biomarker of disease*.

51.3.2 What Are the Subsets of Dupuytren Disease?

At the 2010 Miami Dupuytren Symposium open discussion session, Dr. Ilse Degreef discussed the research relevance of biologically distinct importance of subsets of Dupuytren Disease. She gave the example that noting the type of diabetes mellitus (1 or 2) is necessary for meaningful discussion about diabetes. She described her choice of the Abe score of Dupuytren severity (Abe et al. 2004) to select patients at high risk of early recurrence after fasciectomy for study of adjuvant treatment on fasciectomy outcomes. This selection shortened the needed follow-up time and magnified outcome differences between control and test groups (Degreef et al. 2014). Along these lines, consider three common clinical patterns of Dupuytren Disease progression, which for discussion are referred to here as types 1, 2, and 3. *Type 1* is aggressive, early onset (usually diagnosed younger than age 50), frequently progressing to contracture,

frequently recontracting after treatment, frequently associated with disease beyond the palm such as knuckle pads and Ledderhose Disease, and frequently accompanied by a strong family history of Dupuytren contracture. This subset has been referred to as Dupuytren diathesis. *Type 2* is less aggressive, later age of onset, less frequently progressing to contracture, slower to recontract after treatment, and less frequently associated with disease beyond the palm or a family history of Dupuytren contracture. This is the most common subset treated with a procedure. *Type 3* has minimal physical findings, may regress, does not progress to severe contracture, and is rarely associated with disease beyond the palm. This clinical subset may be unrelated to Dupuytren biology, such as diabetic stiff hand syndrome. What proportion of patients fall into these categories? Do these subsets reflect core biologic differences? Are we grouping together biologically very different diseases simply because they look similar? If we don't know what we are treating, how can we expect to make progress in treatment? *We can't begin to answer any of these questions without biomarker-guided research.*

51.3.3 What Are the Risk Factors for Different Subsets of Disease?

Intrinsic and extrinsic factors each appear to play a role in both the risk of developing Dupuytren Disease and the aggressiveness of Dupuytren contracture progression (Fig. 51.5). These are clues based on clinical experience, but *clinical risk factors lack the specificity and quantifiability of laboratory disease biomarkers.*

51.3.4 What Is the Best Definition of Disease Severity or Aggressiveness?

Treatment-resistant Dupuytren contracture is generally thought to have a genetic basis, but without a genetic or other biomarker measure,

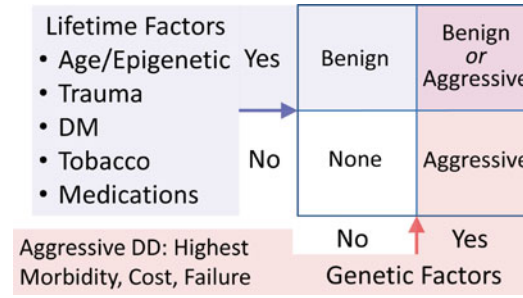

Fig. 51.5 Intrinsic and extrinsic influences on Dupuytren diagnosis and presentation. Both inherited and lifetime exposure factors influence patterns of Dupuytren Disease incidence and severity

the likelihood of progression and recurrence can only be roughly estimated. What is the best single index of disease severity? *Rate of progression of contracture* is an attractive candidate, but is inconsistently documented in most medical records, and may be influenced by temporary extrinsic factors such as vibration exposure, stress of heavy manual labor (Descatha et al. 2012), medications, tobacco, and alcohol exposure (Godtfredsen et al. 2004). Simplified rate-of-progression measures can be represented as durations, such as birth-to-onset (age of diagnosis), onset-to-first-treatment, and treatment-to-recurrence. *Quality of life measures* are also an important consideration, but present two problems. The first is that quality of life measures don't correlate well with contracture severity (Jerosch-Herold et al. 2011). The second is that the relationship of such patient-reported measures to long-term outcomes and disease progression are yet unknown. *Severity of contracture* is a poor isolated index of disease aggressiveness because it is influenced independently by duration of untreated disease, rate of progression, and effects of prior treatment. The *number of procedures or recurrences* is an imperfect index because it is influenced by the category of procedure (minimally invasive, fasciectomy, dermofasciectomy), duration of disease, and the treating physician's personal technique. In contrast to all of these, *biomarker-based assessment holds the best promise of a quantifiable index of ongoing disease activity.*

51.3.5 What Is the Basis of the Relationship Between Dupuytren Disease Severity and Non-Dupuytren Health Risks?

Dupuytren contracture has been reported as a risk factor for both malignancy and early mortality (Gudmundsson et al. 2002; Macaulay et al. 2012; Mikkelsen et al. 1999; Wilbrand et al. (2000, 2002, 2005); Zyluk et al. 2014). The effects of shared comorbid influences and relationships of cause and effect are currently speculative. This may be the strongest case for the potential role of Dupuytren biomarkers. *Biomarker-guided preclinical diagnosis and intervention may change not only the natural history of Dupuytren Disease but also the risk of other life-threatening conditions*.

51.4 What Chronic Disease Research Model Would Be Appropriate for Dupuytren Research?

One logical stepwise approach would be as follows. This outline is the basis of the International Dupuytren Data Bank (Eaton 2016).

51.4.1 Study the Natural History of Dupuytren Disease Over Time with Ongoing Surveys

Because of the large variation in presentation and progress, a large longitudinal study is needed, documenting the course of thousands of patients. Because individual surgeons typically treat only a few dozen Dupuytren patients each year, a study of this size would exceed the capacity of even a very ambitious surgical registry design. However, web-based, direct-to-patient surveys could easily fulfill this requirement, as well as include patients who might not be included in a typical practice-based registry study.

51.4.2 Identify Clinical Disease Subsets

Because there is not yet a standard metric of disease severity, surveys should include a variety of assessments of disease severity, including diathesis markers, duration of disease, interval from diagnosis to first treatment, and Dupuytren-specific quality of life measures. Longitudinal follow-up surveys are needed to use rate of progression as an index of disease severity.

51.4.3 Identify Biomarkers to Track These Subsets and Their Responses to Treatment

Most Dupuytren biomarker research has been of fasciectomy tissue biopsy samples. While valuable, this biases the cohort, excluding patients not undergoing surgery, and has focused on local biology rather than circulating biomarkers. Blood has many advantages for Dupuytren biomarker study. A central blood biorepository geared for open access would be an ideal resource for multiple investigations.

51.4.4 Identify Biologic Targets for These Subsets

Once biomarker-tagged biologic subsets can be identified, research can focus more effectively on identifying molecular targets for drug development or repurposing.

51.4.5 Develop Individualized Disease-Modifying Treatment

The success of molecular targeting for drug development has been demonstrated in many arenas, including the development of statins, TNF-alpha-blockers, imatinib, and many other breakthrough drugs. The same needs to be done for Dupuytren Disease.

51.5 Clues for Future Research Exist, Based on a Large Single Practice Review

I introduced the technique of needle aponeurotomy to the USA in 2003. As a result, my practice rapidly became a center for this procedure, and I treated nearly 1000 Dupuytren hands each year with this technique. Realizing that this was an opportunity for data collection, I added research-oriented Dupuytren-specific questions to my new patient intake forms using a standard form based on initial telephone interview. In addition to typical Dupuytren demographics, patients were surveyed on novel topics of interest, including quality of life ("how much does Dupuytren interfere with the use of your hands?"), genetic (parental age at the time of the patient's birth), symptoms of pain and itching in Dupuytren areas, and others. A total of 3396 unique intake records were available for review in electronic format, of which 3120 records satisfied criteria for completeness. I used custom text processing software to create a de-identified spreadsheet of data retrieved from these records. Data trends were analyzed using Watson Analytics (http://www.ibm.com/analytics/watson-analytics/). This provided a basis to explore and troubleshoot data analysis as pilot work for applying chronic disease research tools to the study of Dupuytren Disease. This was a select group of patients with known biases and is not definitive. Many patients had multiple prior Dupuytren treatments, interest in alternative treatment options, and socioeconomic status which allowed them to travel for specialty care. Almost all patients in this group had scheduled their initial evaluation with needle aponeurotomy in mind. The retrospective data from this cohort is presented here to explore relationships, illustrate concepts, and develop recommendations for future prospective clinical research. What follows below is based on this data exploration, which also guided development of the International Dupuytren Data Bank (Eaton 2016).

The demographics of these patients are profiled in Figs. 51.6, 51.7, and 51.8. Men comprised the majority (77 %), with an average age of 64 and an average age of onset of 53. Women represented 23 % of the group, with an average age of 66 and an average age of onset of 56. The majority of patients had a duration of disease between 1 and 10 years. Record review of patients who returned for more procedures years after their first interview demonstrated variability in reported age of onset and recollection of duration since the prior procedure. *Recommendation*: *offset the unreliability of self-reported clinical durations by repeating questions on dates and durations in longitudinal follow-up surveys.*

28 % had previously been treated for Dupuytren contracture in the symptomatic digit (s), a different area, or both. The majority of previously treated patients requested treatment for recontracture after a variety of prior treatments. Recontracture demographics followed two trends. Recontracture was more common in patients with

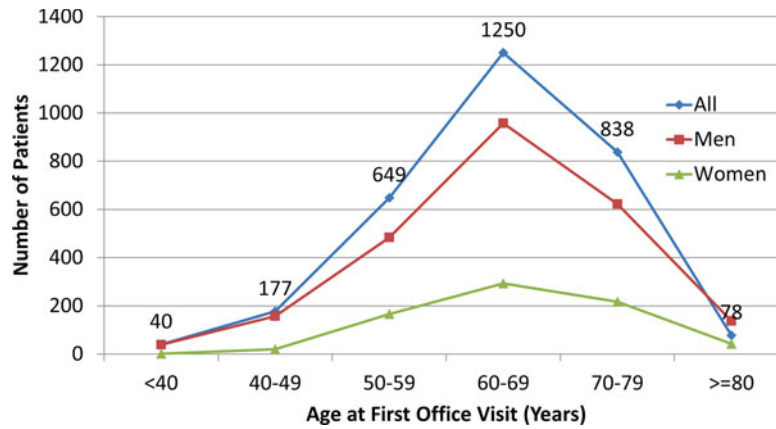

Fig. 51.6 Single practice data showing Dupuytren patient distribution by current age. Age at the time of first evaluation is shown overall and also separated by gender. 90 % of patients were between 50 and 80 years old. The most common age range at the time of evaluation was 60–69 years old

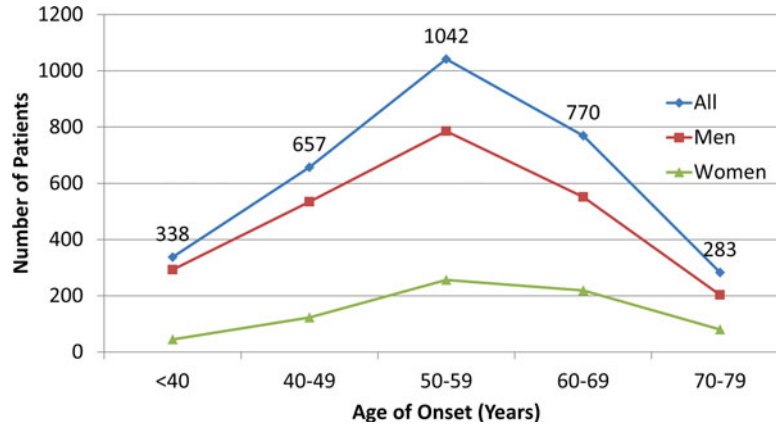

Fig. 51.7 Single practice data showing Dupuytren patient distribution by age at the time of initial diagnosis of onset. Age at the time of first diagnosis is shown overall and also separated by gender. One third of all patients were first diagnosed when between 50 and 59 years old

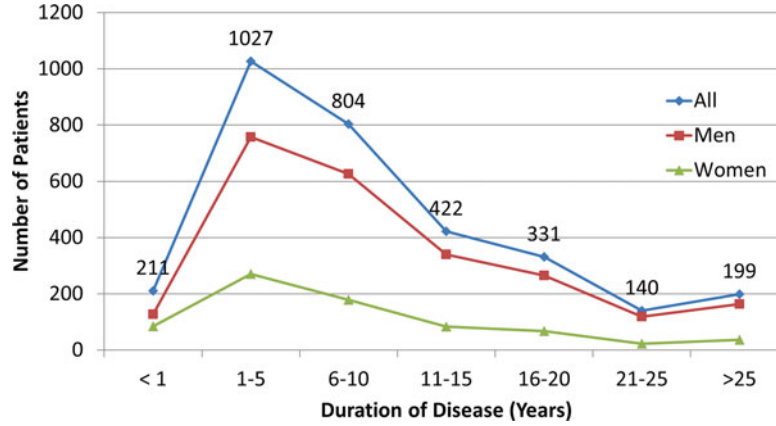

Fig. 51.8 Single practice data showing Dupuytren patient distribution by duration of disease. Duration of disease ((current age)–(age of onset)) at the time of first evaluation is shown overall and also separated by gender. 58 % of patients had a disease duration between 1 and 10 years. One in five patients had a disease duration greater than 15 years when first seen, many of whom had already undergone treatment

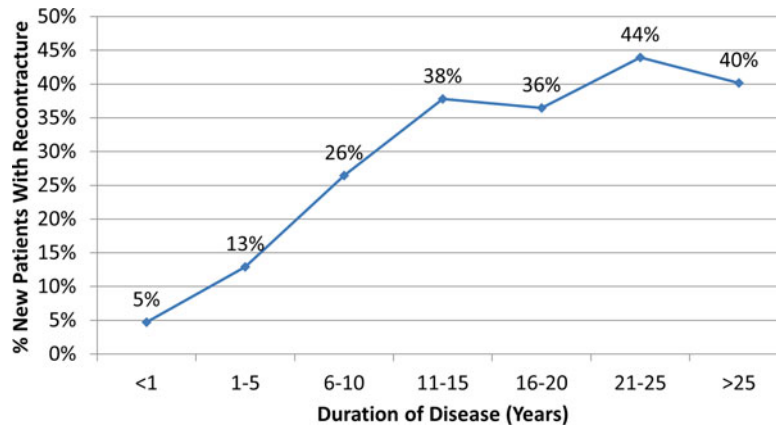

Fig. 51.9 Single practice data showing prevalence of patients presenting for treatment of recontracture following initial treatment elsewhere, categorized by disease duration. 28 % of Dupuytren patients new to this practice were seeking treatment for recontracture. The overall likelihood of presentation for treatment of recontracture was greater in patients with a longer duration of disease

longer duration of disease (Fig. 51.9). Recontracture was also more common in patients with earlier age of diagnosis (Fig. 51.10). The combined effects of a longer duration of disease and greater disease aggressiveness in those with early presentation of disease overlap. *Recommendation*: *further work is needed to identify relationships between age of onset*, *duration of disease*, *and age at time of evaluation on Dupuytren assessment.*

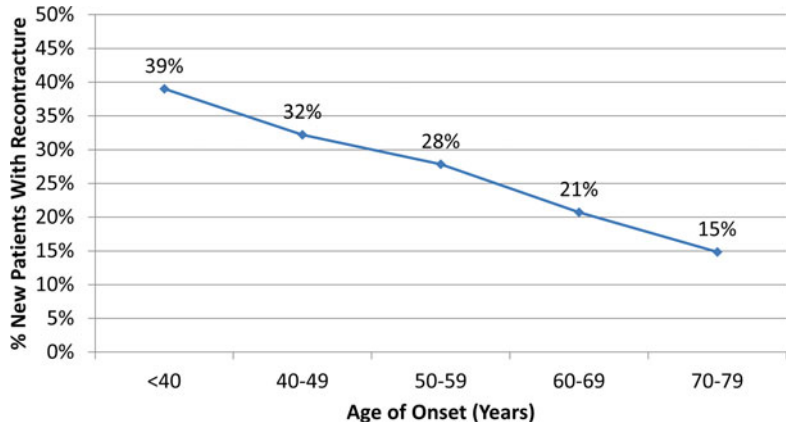

Fig. 51.10 Single practice data showing prevalence of patients presenting for treatment of recontracture following initial treatment elsewhere, categorized by age of onset of disease. The overall likelihood of presentation for treatment of recontracture was greater in patients with earlier age of onset. This represents combined effects of a longer duration of disease and greater disease aggressiveness in those with early presentation of disease

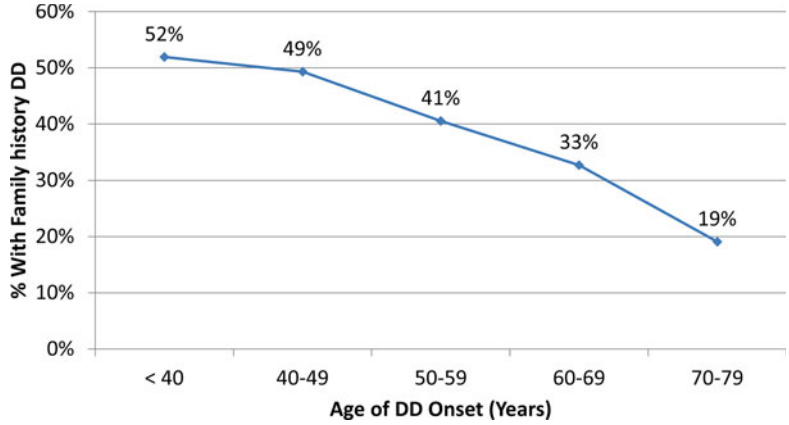

Fig. 51.11 Single practice data correlating family history and age of onset of Dupuytren Disease. Overall, 40 % of Dupuytren patients reported a family history of disease. The prevalence of family history of Dupuytren Disease increases with earlier age of onset of Dupuytren Disease, suggesting that aggressive, early-onset Dupuytren Disease may be a genetically different disease subset than late-onset, less aggressive Dupuytren Disease

40 % knew of a close relative with Dupuytren Disease. 43 % of women reported a known family history compared to 39 % of men. Early age of onset correlated with family history of disease (Fig. 51.11). One consistent observation was that patients who reported no family history in the initial telephone interview often remembered or were reminded of a Dupuytren relative which they then reported in their office visit. *Recommendation*: *offset the unreliability of self-reported family history by suggesting that patients discuss the family Dupuytren history topic with relatives in preparation for follow-up surveys.*

10 % of male patients reported Peyronie disease. Peyronie disease is underreported in medical records, and the patient-reported incidence of Peyronie disease varies from 0.5 to 13 %, depending on how clearly Peyronie disease is described in the questionnaire (DiBenedetti et al. 2011b). Although an association between Dupuytren and Peyronie disease has been suggested, a strong statistical relationship has yet to be demonstrated

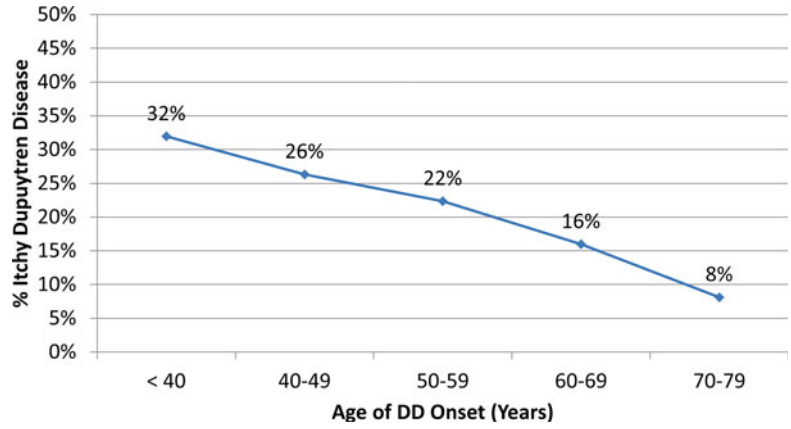

Fig. 51.12 Single practice data correlating Dupuytren itching and age of onset. Overall, 21 % of patients reported itching in areas affected by Dupuytren Disease. This data shows that itching is associated with early age of onset and may provide clues to the biology of aggressive Dupuytren Disease

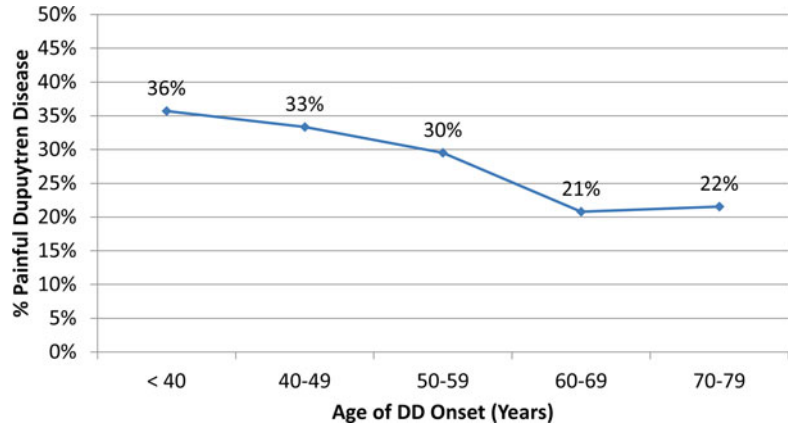

Fig. 51.13 Single practice data correlating Dupuytren pain and age of onset. Overall, 28 % of patients reported pain in areas affected by Dupuytren Disease, more common than typically reported. Pain on Dupuytren area is associated with early age of onset and may provide clues to the biology of aggressive Dupuytren Disease

(Eaton 2014). Meaningful data on self-reported Peyronie disease requires surveys to include questions of prior diagnosis, prior treatment, and explicit clinical description such as "lump or bump under the skin of the penis or significant bend or curve in the penis" rather than simply asking whether the patient has ever had Peyronie disease. *Recommendation*: *if it's worth asking about Peyronie disease*, *it's worth explaining what Peyronie disease is*. The same is true for Ledderhose, frozen shoulder, and Garrod pads.

21 % reported that their Dupuytren areas itched, and 28 % reported pain in areas affected by Dupuytren Disease. These symptoms correlated with age of onset (Figs. 51.12 and 51.13) and may provide clues to the biology of early Dupuytren Disease. *Recommendation*: *longitudinal surveys of Dupuytren symptoms should include specific separate questions regarding pain and itching in Dupuytren affected areas.*

23 % reported concurrent Ledderhose Disease. Ledderhose was reported in 29 % of Dupuytren patients *with* a family history of Dupuytren Disease, compared to 19 % of Dupuytren patients *without* a family history of Dupuytren Disease. Ledderhose diagnosis was also more common in patients with earlier age of onset of Dupuytren Disease (Fig. 51.14). Anecdotally, many patients with both diagnoses reported Ledderhose appearing either years before or years after Dupuytren diagnosis. Ledderhose age of onset may carry similar predictive significance as Dupuytren age of onset. *Recommendation*: *longitudinal surveys of Dupuytren symptoms should*

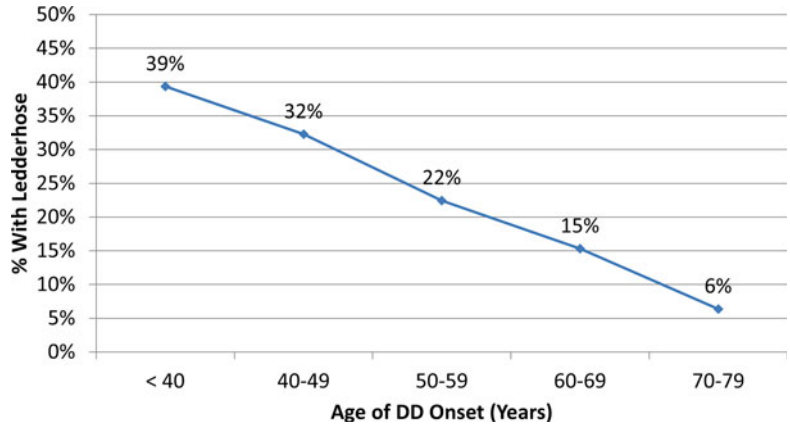

Fig. 51.14 Single practice data correlating Ledderhose prevalence and age of onset of Dupuytren Disease. Overall, 28% of patients reported concomitant Ledderhose Disease. Ledderhose Disease is more common in patients with an earlier age of onset of Dupuytren Disease as well as those with a family history of Dupuytren Disease, suggesting a direct relationship with more aggressive Dupuytren biology

include specific questions regarding the presence and timing of Ledderhose Disease.

10% had a diagnosis of diabetes mellitus, and 3% were on insulin for diabetes. Comparable figures for the general US population are 8.3 and 2.6% (CDC1 2012, CDC2 2011). Diabetes is a known risk factor for the diagnosis of Dupuytren Disease but, based on these numbers, may not proportionately increase the risk of Dupuytren *contracture. Recommendation*: *Dupuytren surveys investigating the role of diabetes need to include detailed diabetic information*, *such as duration of diabetes and duration of both insulin and non-insulin-based treatments.*

11% reported a history of frozen shoulder. Prevalence of frozen shoulder did *not* follow a trend associated with age of onset of Dupuytren Disease. Frozen shoulder was reported in 17% of diabetics compared to 10% of nondiabetics and was over twice as common in women (18%) as men (8%). These trends of diabetes and gender influence on frozen shoulder follow known patterns, but prevalence in all groups is greater than what would be expected in the absence of Dupuytren Disease. Conversely, frozen shoulder has been previously reported as a risk factor for Dupuytren Disease (Smith et al. 2001). However, the lack of association with Dupuytren age of onset as well as the disproportionate relationship with diabetes and gender suggests that the relationship between Dupuytren Disease and diabetes may be unique. *Recommendation*: *biomarker research of Dupuytren Disease should investigate the triad of Dupuytren*, *diabetes, and frozen shoulder as a distinct biologic subgroup*.

51.6 How Might Biomarker-Guided Treatment Impact Dupuytren Care?

Based on experience with other chronic diseases, it's reasonable to speculate that accurate biomarkers and effective targeted molecular intervention could change the approach to Dupuytren Disease in three ways.

51.6.1 The Treatment Algorithm Could Be Simplified, with Less Uncertainty for the Wait and Watch Approach

Accurate disease staging with biomarkers would reduce the uncertainty of treatment indications. Patients with laboratory evidence of low disease activity could be observed, knowing that their chance of progression was low. Medical treatment could be individualized to patients with high biomarker disease activity as preventative or adjuvant treatment (Fig. 51.15).

51.6.2 Preventative Care Could Be Used to Slow the Rates of Progression, Recurrence, and Extension

Patients with biomarker evidence of high risk of progression might reduce long-term risk with prophylactic care. Dupuytren contracture progression

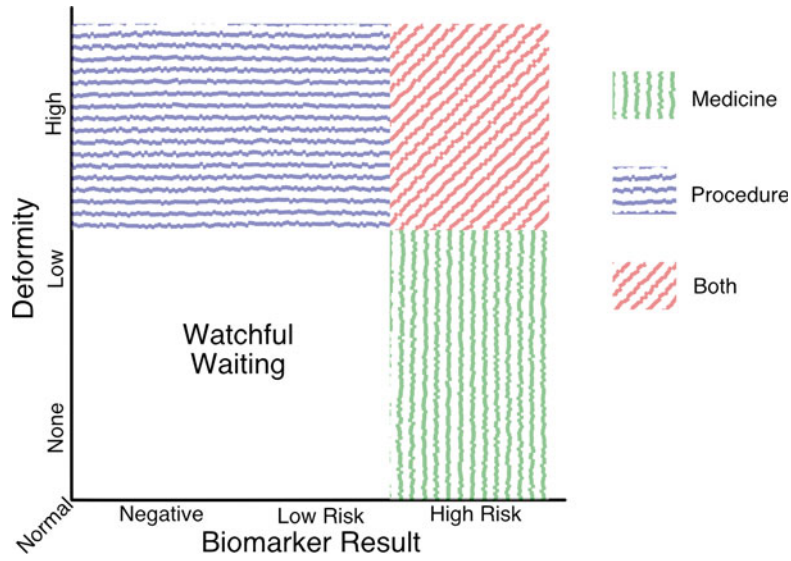

Fig. 51.15 Concept of biomarker-guided individualized medical therapy for Dupuytren Disease. In the hypothetical scenario of a reliable biomarker and available medical treatment, patients would be managed in a consistent fashion by either observation, medical treatment, contracture procedure, or contracture procedure with adjuvant medical treatment. Choice of treatment would be determined by staging, based on biomarker assessment of disease activity and severity of contracture

is often episodic. Biomarker surveillance could possibly prompt treatment as needed to prevent flares of disease activity rather than as continuous suppression.

51.6.3 Suppressive Treatment Could Reduce the Need for Procedures

If suppressive care is effective, the percent of patients requiring procedures for deformity would be reduced, similar to the reduction in the need for rheumatoid hand procedures after the introduction of anti-TNF-alpha biologics.

51.7 What Evidence Already Exists for Dupuytren Biomarkers?

Tissue biomarkers of Dupuytren contracture have demonstrated Dupuytren-specific abnormalities in immune cell composition (Meek et al. 1999), mesenchymal stem cell composition (Hindocha et al. 2011), DNA and gene expression (Shih et al. 2012), mechanical characteristics (Millesi et al. 1995), cytokines (Brenner et al. 1996), and collagen metabolism-related enzymes (Ulrich et al. 2003), in addition to well-known histologic and ultrastructural changes associated with established contractures. These local biopsy findings are important clues. However, palmar biopsy is not practical as a screening test, and not all of these can be assayed as a blood test.

Table 51.2 Potential circulating Dupuytren biomarkers

IgA immune complexes (Houghton et al. 1983)
Autoantibodies to type 1 collagen (Menzel et al. 1994)
Autoantibodies to elastin (Menzel et al. 1994)
DR+ T cells (Gudmundsson et al. 1998)
CD5+ B cells (Gudmundsson et al. 1998)
Matrix metalloproteinase-2, matrix metalloproteinase-14, tissue inhibitor of metalloproteinase-14 (Wilkinson et al. 2012)
Fibrocyte levels (Iqbal et al. 2014)

In addition to DNA and gene expression markers, this list of candidate disease activity biomarkers is based on published research

Circulating biomarkers of Dupuytren Disease have been reported, many as single reports without follow-up or confirmatory studies by other groups (Table 51.2). These include the following: *circulating IgA immune complexes* (Houghton et al. 1983), *autoantibodies to type 1 collagen* and *autoantibodies to elastin* (Menzel et al. 1994) which varied over time, *DR+ T cells and CD5+ B cells* (even higher correlation when both Dupuytren and Ledderhose were present) (Gudmundsson et al. 1998), unnamed disease-

associated *low molecular weight circulating proteins* (O'Gorman et al. 2006), and increased levels of circulating *fibrocytes* (Iqbal et al. 2014). Abnormal tissue levels and ratios of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinase (TIMPs) have been reported in Dupuytren contracture (Wilkinson et al. 2012). Combining this with reports of abnormal levels and ratios of plasma *MMPs* and *TIMPs* as disease activity biomarkers of congestive heart failure (George et al. 2005), lung cancer (Hoikkala et al. 2006), and hepatic fibrosis (El-Gindy et al. 2003), this is a promising possibility as well.

51.8 What If Biomarkers Aren't Found?

Or what if biomarkers don't lead to development of safe and effective Dupuytren pharmacotherapy?

Longitudinal, large, long-term survey-based study of Dupuytren Disease will still provide valuable insights into the natural history of Dupuytren Disease and clarify clinical disease subsets. Such information is still needed to refine existing treatment protocols and evaluate long-term outcomes of yet undiscovered approaches to this difficult disease. Open access to large data sets will provide a lasting resource for future research and researchers.

The biology is complex, but this does not mean that Dupuytren Disease is beyond understanding. There are likely overlapping disease subsets with overlapping risk factors (Rehman et al. 2011). The slow clinical course of Dupuytren contracture may reflect a minor variation in biology, a few percentage points from normal accruing slowly over years. As with all biological processes, a cascade of seemingly unrelated factors may be involved. For example, consider this hypothetical scenario which is based in part on known events: a problem with the molecular assembly of elastin (hypothetical) may provoke a mild elastin autoimmune response (Menzel et al. 1994) which over years degrades elastin, resulting in mechanical changes in the fascia (Millesi et al. 1995) which under specific local anatomic conditions (Satish et al. 2012) creates a mechanical environment which provokes myofibroblast differentiation and activity (Cockerill et al. 2015) which continues until the mechanical stresses are normalized by the effects of deformity (Verjee et al. 2009). This is complex, but not unsolvable: several pieces of the puzzle currently exist. Ultimately, the only time to stop research for a medical cure is when a cure is found. Ignorance is an obstacle to cross, not the end of the road. Eventually, the mystery will be solved.

Conclusions

- Real progress requires a different approach to Dupuytren research.
- Dupuytren Disease is a chronic progressive medical disease with episodic activity resulting in the late complication of deforming anatomic changes. Disproportionate focus on the local complication of Dupuytren contracture has slowed progress in understanding and treating the underlying process of Dupuytren Disease.
- Research must focus on the Dupuytren subset with aggressive disease biology. Patients in this subset are most likely to fail treatment, have greater morbidity from both treated and untreated diseases, and face increased risk of associated conditions including cancer and early mortality. This group has the greatest need and has the greatest potential to provide insights into disease biology.
- Recommendations for application of chronic disease research tools to Dupuytren Disease:
  - Study the natural history of Dupuytren Disease over time with ongoing surveys.
  - Identify clinical disease subsets.
  - Identify biomarkers to track these subsets and their responses to treatment.
  - Identify biologic targets for these subsets.
  - Develop disease-modifying treatment as has been done for other chronic diseases.
- Recommendations based on evaluation of single practice survey data:
  - Longitudinal data from repeated surveys is more accurate than single survey data to document personal disease time line and family history.
  - Data capture of other conditions such as Peyronie, Ledderhose, frozen shoulder,

and Garrod pads is more reliable if the survey includes a simple clear description of the condition and images, if appropriate.
- Form data validation and repeated beta testing is essential for accurate data collection.
- Data quality is improved if the patient is given a preliminary notice that questions will be asked regarding uncommon topics, such as family history, parental ages, and personal medical history.
- Visual data exploration using online tools such as Watson Analytics is helpful for surgeons with limited experience with statistical package software.
- There is great patient interest in participating in research to improve treatment options for Dupuytren Disease.

In summary, technique-oriented surgical research has led to improved procedures for Dupuytren contracture, but has not improved the long-term outlook for Dupuytren Disease or its systemic comorbidities. A strong case can be made to use chronic disease research tools to develop new long-term treatment of Dupuytren Disease and to assess the effectiveness of adjuvant treatment. Biomarker identification plays a critical role in treatment research to identify, categorize, and guide treatment of different subsets of disease. Biomarker screening may allow treatment of preclinical disease to avoid the worst complications of Dupuytren Disease biology. Recommendations for study design are given based on data review of a large Dupuytren practice and the design of the International Dupuytren Data Bank, a large crowdsourced Dupuytren research study presented elsewhere in this book (Eaton 2016).

Conflict of Interest Declaration The author has no conflicts of interest relating to this publication or related materials.

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The Future of Basic Dupuytren Disease Research

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52.1 Dupuytren Disease Research in the Twentieth Century

It is more than 50 years since J.T. Hueston, R.M. McFarlane, and others initiated new research programs focused on optimizing the treatment and understanding the pathogenesis of Dupuytren Disease (Hueston 1962; Luck 1959; McFarlane and Jamieson 1966). While we have seen the development of some new treatment alternatives, our understanding of the molecular pathogenesis of this fibrosis has remained at a rudimentary level. The central aim of basic Dupuytren Disease research is to gain a detailed mechanistic understanding of how complex genomics interact with unique aspects of the palmar fascia microenvironment to cause fibrotic disease development, progression, and recurrence. One way to achieve this aim is to create representative models of Dupuytren Disease development in the laboratory. Such models could be used to identify novel therapeutic targets and provide test beds for optimizing these interventions. To achieve these models, we will need researchers with cutting-edge skills. While diverse arrays of skills are likely to be required, experts in the following three areas may be essential.

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52.2 Tissue Engineering

Tissue engineers will be needed to develop representative and reproducible models of Dupuytren Disease in the laboratory. The poorly defined and complex genomic traits that predispose individuals to develop Dupuytren Disease are unlikely to be replicated in nonhuman animal models. For this reason, the concept of engineering palmar fascia-like tissues in the laboratory and populating them with human cells carrying these complex traits is an attractive option. These models will require careful engineering to replicate the normal and fibrotic palmar fascia environment as closely as possible. They will need to utilize three-dimensional culture substrates with biomechanical properties that are similar to normal or fibrotic palmar fascia. As the palmar fascia experiences physiological stresses during normal hand use, these models should also be designed to receive such periodic stresses. These culture substrates must be suitable for "conditioning" with the complex mixtures of proteins and other molecules found in the extracellular matrices of normal and fibrotic palmar fascia. Finally, and most importantly, these models will not only need to replicate palmar fascia pre- and post-disease development, they will also need to replicate disease *development*, i.e., the transition process from visibly unaffected to fibrotic palmar fascia. This might be achieved by providing pro-fibrotic stimuli to induce cellular structures that are analogous to nodules or contracture cords to develop in long-term cultures. For example, studies have linked the presence of inflammatory cytokines to nodule development (Verjee et al. 2013), and the prevalence of Dupuytren Disease is increased in patients with otherwise unrelated immune-mediated diseases (Patel et al. 2014). While the list of requirements for such models is daunting, they are nonetheless essential if we hope to achieve a representative and reproducible test bed for the development of new therapeutic interventions. Human tissue-engineered models have already begun replacing animal models for preclinical testing and drug discovery (Ranga et al. 2014; Gohl et al. 2014; Tevlin et al. 2015), and individuals with skills in developing these models could be invaluable for advancing Dupuytren Disease research.

52.3 Computational Biology

In parallel with the ability to replicate Dupuytren Disease in the laboratory, we will also need to able to collate and process very large data sets. These data sets may be derived from a variety of sources, including genomic analyses derived from laboratory models of Dupuytren Disease development and computer models of cellular behaviors and responses to stimuli in these models based on engineering control theory. They may also be derived from disease-specific surveys such as the International Dupuytren Data Bank and genomic analyses such as those generated by genome-wide association studies of affected populations. If the recent past is any indication of the future, this area in particular is likely to advance very rapidly. If we hope to take advantage of the ongoing progress in bioinformatic-associated technologies and achieve some of the major goals of Dupuytren Disease research, such as the ability to predict the development of disease in patients before any overt symptoms are evident, we will need to attract researchers with expertise in this area.

52.4 Epigenetics

Unraveling the complex genetics of Dupuytren Disease is now a focus of several research groups. These analyses will identify the single nucleotide polymorphisms, copy number variations, and other mutational changes in the DNA that predispose individuals to develop Dupuytren Disease. As these DNA modifications are heritable components of the germ line, they are predicted to be evident in every nucleated cell in these individuals, including the cells in non-fibrotic and fibrotic palmar fascia. Additional, non-mutational changes to the genome are required for non-fibrotic palmar fascia to transition into the fibrotic palmar fascia that characterizes Dupuytren Disease. These epigenetic changes include modifications in DNA

methylation, and in the acetylation and methylation of histones, the protein "spools" around which chromosomal DNA is wound as chromatin. Such modifications can have profound effects on gene transcription, disease-associated signaling pathway activation, and cellular sensitivities to biomechanical stimuli. We know very little about the epigenetic modifications associated with the development of Dupuytren Disease. Research in this area will be particularly valuable to help us understand the *process* of disease development, as it will supplement current research into the genetic changes that *predispose* individuals to undergo this process. Epigenetics is a now major research focus in other sclerotic/fibrotic diseases (Ciechomska et al. 2014; Tzouvelekis and Kaminski 2015), and we will need individuals with skills in this area to enhance our understanding of Dupuytren Disease development.

52.5 Dupuytren Disease Research in the Twenty-First Century

We cannot hope to understand complex conditions like Dupuytren Disease using simplistic cell culture methods developed in the previous century. By embracing current technologies to develop engineered palmar fascia in the laboratory, manage the large data sets that these models and population-based research programs will generate, and understand the epigenetic processes that regulate disease development in genetically predisposed populations, the next 50 years may finally see the development of truly effective treatments for patients suffering from this intractable disease.

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How Should We Fund Basic Research of Dupuytren Disease?

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Contents

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53.1 What Types of Research Should Be Funded?

The first question to consider when thinking about how to fund future research into Dupuytren Disease is what type of research do we wish to perform? Translational research covers the entire spectrum from basic laboratory research into fundamental genetics, cellular signalling pathways and cell biology; through epidemiological studies of environmental predisposition to disease; past studies of new potential treatments or preventative strategies (often first-in-man studies); to comparative studies of current treatments to determine the cost-utility of each form of treatment. All of these areas of enquiry have merit, and each can make a contribution to the understanding of Dupuytren Disease; so how can we prioritize which areas are funded?

Who should be driving the research agenda? It is my strong belief that our research agenda should be determined in a collaborative fashion. In the UK, the British Society for Surgery of the Hand (BSSH) will shortly be launching a James Lind Alliance Priority Setting Partnership in hand surgery. The James Lind Alliance (http://www.jla.nihr.ac.uk) is a nonprofit-making organization that brings together patients, carers and clinicians to identify and prioritize the top 10 uncertainties or unanswered questions in an area of healthcare. This exhaustive collaborative effort will guide research within hand surgery in the

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coming years. The emphasis on patient involvement within the project at every stage ensures that researchers are tackling questions of true importance to the people affected by the disease.

53.2 Collaboration

Collaboration is not only important in determining the research agenda within a particular field but also in the design and execution of specific research projects. To this end, Dupuytren Disease research demands a particularly varied set of personnel in order to be effective. Of course, the patient must be at the heart of our research, and as a surgeon, I feel that we are also well placed to lead investigations into treatments for our patients. Hand therapists are experts in the rehabilitation of the hand after any form of treatment and are therefore a vital member of the research team. Radiotherapists bring their own expertise and must be encouraged to trial their promising preventative treatment in a rigorous randomized controlled trial. Any clinical trial must be designed with expert statisticians, trial methodologists and a team of research nurses. Basic science studies need experts in genetics, epidemiology, cell biology and medical engineering. As we collect ever-larger datasets, bioinformatic skills will become increasingly important.

53.3 Conventional Funding Streams

The type of organization that funds our research varies depending on the type of study. For basic science studies, large charities and governmental organizations are the traditional major funders. In the UK, these include the Wellcome Trust and Medical Research Council (MRC); in Europe, the European Research Council (ERC); and in the USA, the National Institutes of Health (NIH). Grants from these funding bodies are extremely competitive, and the chances of success are greatly increased by an impressive track record, a supportive institute and a cutting-edge project, especially with promising preliminary data. Pump-priming grants from smaller organizations (e.g. BSSH, Royal College of Surgeons) can be invaluable in making a successful application for larger grants.

Translational projects, including first-in-man studies and early phase clinical trials, are often funded by similar organizations to those funding basic science. In addition, the role of the professional societies in backing their members to produce pilot studies and allow applications for more substantial funding is even more important at this stage.

Large-scale clinical trials, in particular comparative trials of established treatments, are very expensive, with costs often upwards of £1 M ($1.54, €1.39). This requires funding from well-resourced governmental organizations such as the NIH, ERC or the National Institute of Health Research (NIHR) in the UK. The funding streams here are extremely competitive and will often only address questions of fundamental importance to the nation's health.

Pharmaceutical companies fund research across the spectrum of translation, from basic science to large-scale clinical trials. However, they will only fund research with the potential for commercial gain. The publication bias and selective reporting of industry-funded trials is well documented, and extreme caution must be exercised when interpreting research data that is sponsored by industry.

53.4 Unconventional Funding

Modern technology and social networking has enabled novel funding streams within a variety of industries. Crowdsourcing is the process of obtaining needed funds by soliciting small contributions from a large group of people, especially from an online community, rather than from a traditional funder. This method has worked successfully in other areas of medical research. For example, the American Gut project (http://americangut.org) is the world's largest open-source science project and has raised over $1 M in two years. The UK offshoot British Gut (http://www.britishgut.org) has raised almost

£120,000 in one year. For a charge of £75, volunteers send a faecal sample for analysis, as well as filling in a questionnaire regarding health, diet and lifestyle. Their microbiome and other data are then made available to the individual providing the sample for them to compare with other contributors around the world and also to medical researchers investigating the contribution of the microbiome to disease. It is possible that crowdsourcing may become more common in medical research in the future and could be exploited in Dupuytren Disease. For example, genetic findings that may correlate with the outcomes of surgical or non-surgical treatments could be typed for a fee and the subsequent data made freely available to the research community. Furthermore, Dupuytren Disease patients having a surgical treatment could volunteer for their samples to be shipped to a lab, effectively paying for the costs of preservation and transportation, and thereby allowing their tissue to be used in research rather than being discarded.

Conclusions

In order to fund Dupuytren Disease research in the coming decades, we need to collaborate internationally to answer the questions that are important to our patients. Funding for such research is likely to come through conventional routes, including industrial collaboration. Unconventional funding routes may become more important in the future.

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Clinical Research: International Collaboration to Execute High-Powered Clinical Trials

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Marie A. Badalamente

The closing session at the May 2015 International Conference on Dupuytren Disease and Related Diseases in Groningen, The Netherlands, was on the topic of clinical research. The distinguished panel members of this session were Joseph Dias, M.D., Leicester General Hospital, United Kingdom; Charles Eaton, M.D., West Palm Beach, Florida, USA, and founder of the Dupuytren Foundation; and Steven Coleman, M.D., Brisbane Hand and Upper Limb Clinic, Brisbane, Australia. The session was chaired by Marie A. Badalamente, Ph.D., Stony Brook University Medical Center, Stony Brook, New York, USA.

The purpose of the closing session was not only to provide insights by the panel members on clinical research but also to highlight the processes of research and to offer advice on potential obstacles to research.

The chair's "call to action" began with the following statement "there is no elevator to success. You have to take the stairs." The meaning of this statement is fairly simple in terms of clinical research or, indeed, research in general. Research can be a long and protracted process with peaks and valleys of successes vs. failures. Meticulous scientific method and patience for the method are keys to a successful research endeavor. Collaboration is essential. Expert scientific/medical personnel should collaborate nationally and across borders around the world. Appropriate resources, especially funding sources, are necessary to a successful research program.

Some might think that the "doing" of the research is paramount and this is certainly true. The study development stage is crucial before studies can be implemented. The design of a clinical study must be done in meticulous fashion before the study can be executed. This begins with a well-designed study protocol. As clinical research is often multicentered, the protocol must be in great detail and must be followed by all the investigators test sites. Test sites should never deviate from the study protocol as this injects undetermined variability into the investigation. National and international clinical studies offer the best potential size, scope, and impact of research. The principal investigators at each test site are responsible for the exact execution of the study protocol. The development by principal investigators of a team to implement the study protocol is essential. Members of the team include associate investigators and study coordinators. It is the study coordinator's responsibility not only to attend patient visits, but to enter study data meticulously whether it be by paper records and/or electronic databases. Member nation regulatory guidelines must be followed. In the USA, these guidelines are termed "good clinical

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practice (GCP)." Physical facilities in which the clinical research is performed must be appropriate and allow for easy patient access for necessary and often multiple study visits. The clinic or hospital sites must have enough staffing to help implement the study protocol. Sites must have the appropriate resources such as supplies and equipment necessary to conduct the study protocol. Sites may be required to have more advanced supplies and equipment, depending on the study protocol, and also have the means necessary to treat serious or even life-threatening adverse events.

The safety of the clinical research patients is always essential. This is addressed in the study protocol. Adverse event recording and monitoring for safety must be done in an excellent and meticulous fashion. For serious adverse event(s), within a study, mechanisms should be designed prior to study implementation that allow for immediate treatment of the adverse event, as well as prompt reporting of the adverse event to all study centers and regulatory authorities. Stopping rules within the clinical protocol is sometimes necessary if safety is an issue based on an occurrence of a serious adverse event. A stop (the study) rule may be designed into the study protocol for a short series of patients to be enrolled and studied, after which, if safety is deemed to be verified, then the study may continue. Independent study monitors should be designed into a study to not only verify data entry but also to monitor expected and, if necessary, serious adverse events. In the USA, under Food and Drug Administration regulatory authority, such study monitors in multicenter studies usually visit investigative test sites every 5–6 weeks during the routine course of a study. Study monitors may be hired by the study sponsor but are independent of sponsor input. Contract research organizations may also provide study monitors to verify collected data.

Statistical power analyses and statistical tests should be designed well before the implementation of a clinical study to assure that the purpose of the study is answered with clear statistical significance. Obviously, more statistical power is available if the "n" number of enrolled research patients is high. Collaborations with large data sets are always desirable. It is important to note that most clinical research studies have a primary end point for clinical success. This needs to be designed with utmost clarity. Studies may have multiple secondary end points, also designed with high clarity. Study sponsors provide biostatistical funding. If sponsors do not provide the funding, it is essential to hire statisticians for power analyses and suggestions for statistical tests to be used and for data analysis.

Funding of clinical research is essential and investigators should be creative in seeking funding from ever-diminishing funding sources. All funding sources should be evaluated. These include government sources, as well as industry sources. In the USA the National Institutes of Health (NIH) and, indeed, even the Food and Drug Administration (FDA) offer clinical research grants. For example, the NIH offers a small grant program termed "The R03 program." This provides limited funding for a short period of time for pilot or feasibility studies or collection of preliminary data. Therefore, this may be a pathway to larger amounts of funding for clinical research. Examples in the USA of larger clinical research grants include the R01 funding mechanism or the P30 mechanism. The P30 mechanism is termed a center core grant to support shared resources and facilities by a number of investigators from different disciplines who provide a multidisciplinary approach to a joint research effort. Another example of the NIH larger funding grants is the P50 or the specialized center type of funding to support any part of the full range of a research and development. If investigators believe they have intellectual technology that is worthy of a patent, such as in development of a drug, then consideration should be given to patent filing and association with a biopharmaceutical company for research and development. In the USA when the public research and development spending by the National Institutes of Health was compared to all private biopharmaceutical companies, it was determined that the total NIH budget was only one third of that available from private companies. Therefore, the companies are entirely capable of funding for

such research and development. However, licensing agreements between investigators' institutions and the companies must be in place prior to going forward. Investigator conflict of interest, if applicable, must also be transparent and fully disclosed.

The authors' own personal experience in the development of the Xiaflex/Xiapex (collagenase *Clostridium Histolyticum*) as a nonoperative injection treatment for Dupuytren Disease incorporated many of the basic tenets explained in this chapter. Fortunately, the US Food and Drug Administration approved this treatment in 2010 and the drug is successfully being used around the world.

Conflict of Interest Declaration Consultant to Endo Pharmaceuticals and Actelion Pharmaceuticals; Partial Xiaflex/Xiapex royalty from BioSpecifics Technologies Corp.

Patient-Rated Outcome Measures and Dupuytren Contracture

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55.1 Introduction

Patient-rated outcome measures are now well established in every clinical discipline. The patient is asked a series of questions, and usually a score is calculated to assess the patients' view on how they are. Measuring outcome is important.

As clinicians our desire is to improve our patient's lot. The purpose of our effort is best summarised by Donald Berwick (1997) when he wrote:

> the ultimate measure by which to judge the quality of a medical effort is whether it helps patients (and their families) as they see it. Anything done in health care that does not help a patient or family is, by definition, waste, whether or not the professions and their associations traditionally hallow it.

Lord Kelvin (Thompson 1889) said:

> When you can measure what you are speaking about, and express it in numbers, you know something about it, when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts advanced to the stage of science.

Without assessment of outcome of our treatments, we can only form an anecdotal impression that we are helping patients with our interventions and may not be even aware of the ineffectiveness of our treatments or the harm caused. This is particularly true for the treatments offered for Dupuytren contracture.

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55.2 Objective Outcome and the Surgical Target for Dupuytren Contracture

When surgeons talk about the outcome after Dupuytren surgery, we refer to the narrow surgical target. Our main surgical target is to correct a joint contracture. Our patients also want us to achieve this target with the least loss to them, without any complication that may worsen them, in the shortest time and in the most efficient way.

As surgeons our training and focus is on measuring impairment in range and strength. We assess joint range using goniometry and hand strength using dynamometry. For Dupuytren surgery the outcome is joint range, our outcome is measured using finger goniometry (Engstrand et al. 2012; McVeigh et al. 2016). One study showed that the error rate is 3° but another study showed a 4° intra-rater difference while the difference is far greater between raters. This does need accurate and unbiased goniometry.

But we still do not know simple things. We do not know what degree of correction helps the patient. We do not know the minimal clinically important improvement in the joint contracture, which will benefit the patient. So although we know the target is to improve the range, we do not know how much improvement is going to make a difference to our patients.

Our main concern for the patient is that the joint contractures will recur, but there is no clear definition of recurrence used in published literature. There is now consensus that 20° progression from 6 to 12 weeks to 1 year defines a recurrence (Dias 2015; Felici et al. 2014; Peimer et al. 2013).

Whatever we measure and the closer you look at the method of measurement, we find that the measurement can be flawed. It is easy to assume that we have chosen the correct measurement tool, that it is accurate and lets us assess what is important.

It is easy, when presenting or publishing a paper, to use sophisticated statistical techniques that discount the errors in or relevance of measurements. As clinicians and researchers, we easily accept the "validated" outcome measures, but rarely question whether these measures are truly appropriate for the disorder we are treating and whether the measure is likely to respond to the intervention we are proposing.

Our measurements must help us advise our patient, and this involves asking patients what they think. This requires patients to rate the outcome of intervention. As Berwick said, we need to establish whether our treatment has helped the patient "as they see it".

55.3 Patient-Rated Outcome Measures (PROM)

The best way to do that is to get patients to assess their own outcome. So using patient-rated outcome measures (PROM) asks the patients to judge the value of our intervention. Have we helped them? We ask the patient a series of questions to gauge their views about their own health (Devlin and Appleby 2010). The patient must be completely independent of you as the clinician. The clinician must not prompt the patient or translate questions as this can promote bias in their responses. PROMs allow us to answer the questions: "Can we be sure that spending on health is justified by the output that it produces? And "Are scarce resources being used in a way that maximises their value to patients and society?" A PROM is a clinical endpoint which measures whether the patient is helped or harmed noting how "a patient feels, functions and survives".

55.3.1 PROM Value

The value of PROMs is well established, and research funding bodies look at patient outcome measures as a principal outcome. These outcomes help patients make choices about their treatment. It helps commissioners to measure providers. These questionnaires help us assess if we are delivering good care. Are we improving patients?

It helps link the payment we get to the improvement that we give people. PROMs enable us to monitor and improve and support quality improvement. PROMs assist in regulating the

safety and quality of the service we provide. There are many benefits to using PROMs over and above as a tool to do research. We can no longer depend on objective measures alone.

55.3.2 Patient-Rated Outcome Measures: URAM

The URAM Patient-Rated Outcome Measure (Beaudreuil et al. 2011) is a 9-item 6-interval disability scale developed specifically for patients with Dupuytren contracture in 2011 with examination of its psychometric properties including responsiveness. Our patient user group has confirmed that this questionnaire does reflect their experience of the contracture although they did not find it comprehensive, and it did not capture the impact on the patient of complications of interventions (Dias et al. 2015b).

55.3.3 Patient-Rated Hand Outcome Measures

There are now a few validated hand outcome scores. These include the Patient Evaluation Measure (PEM), the Disabilities of the Hand, Arm and Shoulder (DASH) (Hudak et al. 1996) and the Michigan Hand Questionnaire (MHQ) (Chung et al. 1998, 1999). These three questionnaires have been compared and their strengths and weaknesses explored.

The Patient Evaluation Measure (PEM) is a validated questionnaire (Dias et al. 2001) of 11 items in the Hand Health Questionnaire and three in the overall assessment which includes a transition question. The responses are on a 7-interval scale.

The MHQ was devised by Chung et al. from the University of Michigan in 1998 (Chung et al. 1998), also using psychometric principles. It has 63 questions and measures 6 domains: overall hand function, activities of daily living, work performance, pain, aesthetics and patient satisfaction (12 questions) with hand function. Of these the domains of function and pain refer to symptoms (15 items), those of work and ADL to disability and handicap (22 questions). The scoring system is complex but clearly defined. The right and left hand can be individually assessed. The originators found the MHQ to be valid and reliable.

Often outcome questionnaires are used to give credibility to an audit or research. However, we must investigate the constituent questions within a questionnaire to understand the different themes being explored by each.

Different outcome measures assess different attributes of impairment, disability or handicap. Impairment is the loss of structure or function of anatomy or physiology. Disability is the loss of ability to perform specific activities, while handicap is the inability to perform one's normal role. With regard to the hand outcome PROMs, for example, the DASH covers pain, symptoms, disability and handicap. Questions addressing handicap are over-represented in this questionnaire. Also questionnaires assess impact and satisfaction. Satisfaction is a measure of patient experience with the entire interaction rather than outcome alone. The MHQ is much more detailed and very well constructed. It is the only PROM that differentiates an outcome between the two sides (the others do not), and it also measures different domains. However, it is lengthy and complex and is of great value for research. This is not as effective as a monitoring system where a really simple outcome measure is required.

All these questionnaires have been shown to be useful, reliable, valid and reproducible and in many cases are responsive (Dias et al. 2008).

55.4 Questionnaire Completion Considerations of PROMs

We assume once you have got an outcome measure that it is meaningful.

However, we need to explore this assumption carefully. The responses may not truly reflect what the patient thinks in a substantial number, depending on the population being investigated.

The responses may not reflect the outcome if other considerations have an effect. The patient may not understand the questions, try to please you because they are grateful for what you have

done to them or there is workman compensation, litigation and all that and you have got all the bad end of the score being marked.

Then the questionnaire may reflect a completely different disorder. For example, the patient may have had a carpal tunnel decompression and be cured of their tingling, but when they complete the outcome form, their thumb arthritis is symptomatic so the patient's responses will now reflect new symptoms unconnected to the disorder you wish to assess.

Incomplete questionnaires can lead to missing scores depending on the scoring rules of each questionnaire. The personality type of the respondents can influence completion patterns.

Some patients will always score to one end of the questionnaire or the other; they may be confrontational or very cautious and uncertain, only marking in the middle. Other subjects try to guess what you would like them to say and so overestimate their benefit. Yet others are very literate, they will question the exact purpose of the item.

Older patients may not read the questions and yet hazard a guess. In the UK around 15 % of the population can be "functionally illiterate".

55.5 Practical Issues on PROM Collection

There are many practical considerations to the meaningful use of PROMS. The first is to decide where to collect the outcome, whether in clinics, at the preoperative assessment or at discharge. The next is to ensure that staff knows who is responsible for collecting the forms and making sure that the form is complete. This task can easily be delegated to administrative staff. To collect, enter data and clean data needs personnel and expertise. Finally, the collation of data, its analysis and regular reporting ensure that the data is used rather than just accumulated. The response rate is really important. If most of the subjects of interest do not respond, the data is of no value. For example, young men are particularly difficult with a low response rate expected in this population.

Analysis Good-quality analysis of the questionnaire data and data cleaning requires skilled data managers and statisticians so that the results are as robust as can be. This will permit a sound basis for inference.

55.6 Minimal Clinically Important Difference (MCID)

The minimal clinically important difference (MCID) is the improvement in the score after treatment which is clinically meaningful in that the patient notices a clinical change. It is the smallest difference in the score which the patient perceives as a benefit or a loss. There are many methods of estimating the MCID (Copay et al. 2007).

These can be techniques based on statistical distribution or on anchor questions which assess the transition, usually of the primary symptom or more general assessment of improvement or deterioration of the patient's state. Usually anchor methods using a ROC curve are preferred.

In order to establish the appropriate size of a study population, one needs two items of information: the minimal clinically important difference for whichever outcome measure is chosen and the standard deviation of the measurement in your study population. This will permit the estimation of the effect size and allow the calculation of the power of the study to detect a minimal clinically important difference. For example, if a VAS for pain is used, then 1.4 is the minimal clinically important difference. We do not know the minimal clinically important difference for a correction of Dupuytren contracture. Just as the interpretation of the PROM needs to be approached with caution so also the use of a minimal clinically important difference. It varies between conditions, co-morbidities, different patient groups, genders, ages and ethnic groups. Also the time point after treatment may affect the MCID (Rodrigues et al. 2014).

55.6.1 MCID Patient Evaluation Measure (Dias et al. 2015a)

Using multiple methods (ROC, Distribution, Social Comparison Approach), we investigated the MCID of PEM in 878 patients surveyed 27

months after their first visit. 23 % were women and the mean age was 63 years.

The PEM was collected throughout the treatment. The mean initial PEM was 40 (SD 22), the final PEM was 31 (SD 24), and the improvement in PEM was 8 points. PEM reflected deformity (Pearson's Correlation 0.4) and correlated highly (0.79) with the 7-interval anchor question asking how the hand was, compared to before. Responses ranged from "delighted" to "terrible" with 4 representing "no change". Using ROC (AUC 0.80) and Youden's Index 3 points improvement in PEM classifies if patients will consider that they have improved clinically.

The PEM improved by 3 points over 3 years in the 334 patients who did not have surgery and by 11 points in the 544 patients who had surgery. Around 1/6 of untreated patients worsened which was the same proportion finding that they were worse after surgery.

55.6.2 MCID URAM

Based on a survey of 531 patients with Dupuytren contracture who had a mean PEM at follow-up of 24 (SD 23) and the mean URAMS of 10 (SD 11), we investigated their views on the usefulness of the URAM (Dias et al. 2015b). URAMS had a high correlation 0.78 with PEM and reflected the degree of contracture of the worst affected finger (Pearson's Correlation 0.44). We asked patients if the URAMS captured what was important to them before and after intervention. Around a quarter of patients found that the URAMS did not properly represent the condition of the hand.

The MCID for change for URAMS has been assessed as 2.9 (Beaudreuil et al. 2011).

PEM explained 71 % of the state of the hand after treatment while URAM explained 52 %.

URAMS reflects contracture and disability but may not completely capture the state of the hand after intervention for Dupuytren contracture, (its MCID is 2.9) and so if used should be combined with a Hand Outcome Measure such as the PEM to capture the state of the hand after treatment.

55.7 PROMs for Monitoring

PROMs are of particular use for audit and monitoring. These can be used for assessment of outcome in registries, e.g. the National Joint Registry in the UK. Hand outcome measures are not routinely used for this purpose, and it is unusual for clinicians, unless they are interested in their own outcome, to collect PROM data.

PEMS for Dupuytren contracture has a minimum clinically important difference of 3, which is almost the same as for most hand disorders, and the common hand operations show a good change in score many times their MCIDs. We have also observed that many hand disorders which are not treated but observed show an improvement.

For common musculoskeletal operations such as hip and knee replacements, commissioners assess performance using funnel plots in the UK. The data is at the surgeon level and not the hospital. The patient can look up the surgeon and see whether they are outside 3 standard deviations outside the norm. This would raise an "Alarm" and need immediate investigation. When a surgeon lies between 2 and 3 SD bands, an "Alert" is raised. All the rest of the surgeons are "in control". So collecting patient-reported data presents us with an opportunity and an insight that without data we do not have.

Conclusion

As a clinical and research community, we get the most out of PROMs in several ways. In the end the patients benefit as we offer more effective solutions based on evidence of effectiveness rather than our preference alone.

Conflict of Interest Statement The author has no conflict of interest to declare.

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IDDB: An International Research Database of the Dupuytren Foundation

56

Charles Eaton

Contents

56.1 Introduction

Conceptual hurdles have slowed the development of effective disease-modifying treatment.

56.1.1 Current Dupuytren Treatments Only Address Late Complications

There is no widely accepted early or preventative treatment for Dupuytren Disease. Management is limited to procedures for Dupuytren *contracture*, which is a *complication of Dupuytren Disease*. This parallels the antiquated role of surgery for peptic ulcer disease, anal cancer, pulmonary tuberculosis, iodine deficiency multinodular goiter, and other diseases prior to effective medical treatment. For these and for Dupuytren Disease, surgery is a poor substitute for effective biologic treatment: *disease persistence* limits the success of treatment by procedure alone. From the perspective of disease biology, technical refinements in Dupuytren care have been change without progress: long-term risk of re-contracture after a Dupuytren procedure has not improved in over 50 years. This will only change when treatment exists for the primary disease, not limited to the management of complications. Such treatment is the goal of the IDDB.

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56.1.2 Dupuytren Disease Is Heterogeneous, Not Unpredictable

Dupuytren Disease varies in many areas, including the *subjective* symptoms, the *risk of progression* from diagnosis to contracture, the *rate of progression* from diagnosis to contracture, the *anatomic patterns* of involvement, as well as short- and long-term *outcomes* following contracture treatment. It is possible that, as for many other disorders, these differences reflect biologically different disease subsets rather than random differences in presentation of a single disease. The IDDB is structured to identify unique biologic subsets of Dupuytren Disease.

56.1.3 The Natural History of Untreated Early Disease Is Virtually Unknown

A large body of literature exists documenting disease progression after treatment of Dupuytren contracture. This is a select subset of patients with Dupuytren Disease. In contrast, only a few, some of them very small studies, have reported on the longitudinal history of untreated early Dupuytren Disease (Millesi 1965; Gudmundsson et al. 2001; Reilly et al. 2005; Seegenschmiedt et al. 2012; Lanting et al. 2016). Palmar nodules in some patients regress without treatment. Some patients with minimal changes do not progress to contracture over the course of decades. Some patients do not recur after a single procedure. In some patients, contractures progress intermittently, separated by months or years of stability. Some patients progress from early disease to crippling hand deformities despite the best available treatment. Whether or not these disease patterns actually exist as distinct groups or what proportion of Dupuytren diagnosis these groups represent is not yet known. Data from insurance claims or medical record review is unreliable to clarify this issue because medical records fail to document Dupuytren diagnosis in large majority of patients with early Dupuytren Disease (DiBenedetti et al. 2011). By following individual progress in a large number of Dupuytren patients at all stages of disease, the IDDB will define predictive factor models of the natural history of patients with early Dupuytren Disease.

56.1.4 Dupuytren Biomarkers Are Needed for Meaningful Biologic Research

Therapeutic research requires a comparison of a treated group with a matched control group. Commonly used clinical risk factors (age, sex, family history, age of onset, knuckle pads, Ledderhose, bilaterality, number of fingers, radial hand involvement, smoking, drinking, and manual labor history) remain controversial and of unknown significance regarding prognosis of untreated early disease. Until disease and disease severity biomarkers can be used to quantify the risk of progression of early Dupuytren Disease, the margin of error defining true control groups and the true efficacy of preventative or disease-modifying treatment will remain unknown. The IDDB will identify predictive laboratory biomarkers of Dupuytren Disease severity to facilitate identification of a molecular target for drug development.

56.2 Overview of the IDDB

56.2.1 History

An international research database was proposed at the Miami conference (Eaton et al. 2012). The IDDB was developed as a research program of the Dupuytren Foundation (http://Dupuytrens.org), a US-based 501(c) (3) nonprofit charity established in 2008 to improve the care of Dupuytren Disease and related conditions. The first phase of the IDDB was launched to the public in late 2015 after 3 years of planning and fund-raising (http://dupuytrens.org/enroll-in-the-iddb/). The goal of the IDDB is a cure for Dupuytren Disease.

56.2.2 Models and Precedents

The IDDB is modeled with concepts used in medical research programs successful in developing new treatments that reduce morbidity, mortality, and the need for surgery for chronic diseases. Two programs that influenced IDDB design were the Framingham Heart Study and research leading to the development of tumor necrosis factor-inhibiting biologics.

56.2.2.1 Framingham Heart Study

The Framingham Heart Study of cardiovascular disease (http://www.framinghamheartstudy.org/) examined longitudinal correlations between physical examination, laboratory tests, and cardiovascular disease. This study was the first to identify cholesterol as a risk factor (biomarker) for cardiovascular disease and a potential therapeutic target. The medical term "risk factor" originated from this study. Based on these findings, therapies developed to reduce cholesterol levels led to *biomarker-guided treatment to lower the risk of complications and reduce the need for invasive surgery for complications* of vascular disease. This was streamlined by the fact that cholesterol is both a biomarker and a therapeutic target.

56.2.2.2 TNF-α Inhibitors

Rheumatoid factor was identified over 70 years ago as a biomarker of rheumatoid arthritis. Tumor necrosis factor alpha (TNF-α) was later verified as a therapeutic target (Elliott et al. 1994). Although pharmacologic treatments for rheumatoid arthritis had been in use for years, results were unpredictable and many patients developed progressive deformity requiring surgery despite medical treatment. TNF-α inhibitors as *targeted molecular therapy significantly reduced the need for invasive surgery for hand deformities caused by rheumatoid arthritis.*

56.2.3 Structure and Timeline

The IDDB is organized into three overlapping phases over the course of 5 years. The phases are *longitudinal surveys*, *biospecimen collection*, and *data analysis*.

56.2.3.1 Phase 1: Recruitment, Enrollment, and Longitudinal Surveys (Table 56.1)

Large Study Size A large body of evidence suggests a genetic basis for aggressive Dupuytren Disease. Meaningful progress pinpointing genetic origins of Dupuytren Disease requires a sample size of at least 10,000 affected patients with disease in addition to control data. A minimum enrollment of 1000 control patients will qualify the IDDB to access additional genetic data from NIH genetic archives. These are minimum numbers. Even with an optimistic study completion rate of 50%, this projects to initial enrollment of 22,000 patients.

Direct Patient Enrollment Traditionally, large-scale surgical disease research is organized through a surgical registry. In the registry model, surgeons collect and share data on their own patients treated for a specific diagnosis. The registry compensates the surgeon's practice for cost and staffing involved in registry participation. Assuming as many as 70,000 Dupuytren procedures is performed annually in the USA (a high estimate) and knowing that the American Society for Surgery of the Hand has over 3000 US members (a low estimate of all US doctors performing hand surgery), the average US hand surgeon performs at most two dozen Dupuytren procedures each year. This makes a registry approach impractical for a study of this size. The IDDB uses direct patient enrollment via secure online forms as a more practical and cost-efficient alternative. Using validated tools for self-diagnosis (Pervulesko et al. 2011) and self-reported contracture severity (Dias and Braybrooke 2006), patients need not see a physician to participate (Figs. 56.1 and 56.2). Direct patient enrollment has the additional advantage of including patients not seen by surgeons, such as those with early disease, those pursuing alternative treatment options, and those avoiding consultation, because

Table 56.1 Considerations of IDDB recruitment, initial enrollment, and follow-up surveys

Recruit patients	Enrollment survey	Follow-up surveys
Directly	*Demographics*	*Changes in*
E-mail	Age, sex, race	Social history
SMS	Handedness	Medical history
Social media	Social history	Medications
Newswire	Medical history	Garrod pads
Website	Manual activity	Ledderhose
	Medications	Frozen shoulder
		Peyronie
Indirectly	*Diathesis factors*	*Reassessment of*
Physician/therapists	Family Dupuytren	Disease location
Office brochures	Age onset	Treatment
Branded goniometers	Garrod pads	Current deformity
Conferences	Ledderhose	Quality of life
Publications	Frozen shoulder	
ListServes	Peyronie	
E-mail		*Outlier inquiries*
Dupuytren organizations	*Dupuytren history*	Detailed family tree
Word of mouth	Disease location	Monozygotic twins
	Treatment	Non-Caucasians
	Current deformity	Unusual events
	Quality of life	Alternative treatment

of unpleasant rumors or prior experience with Dupuytren procedures. Data from such patients, or from patients with complicated treatment histories (typically excluded from standard registry models), will be captured through direct enrollment.

Survey Recruitment The IDDB uses a variety of pathways to recruit enrollees, including online tools (e-mail, social media, and website presence) and print patient brochures provided to hand surgeons and therapists (Table 56.1).

Longitudinal Survey Design Enrollment uses secure online forms. The initial enrollment form captures generic demographic information, Dupuytren diathesis factors, personal Dupuytren history, and patient reported assessment of current deformity and quality of life impact of Dupuytren Disease. Follow-up surveys are provided every 6 months thereafter to document progression, treatment, and targeted follow-up of outliers who may provide unique insights, such as those with very aggressive or unusual presentation of disease, dense family history, monozygotic twins, non-Caucasians, and others. Follow-up surveys may also include questions targeting potential associations not included in prior surveys.

56.2.3.2 Phase 2: Biospecimen Collection

Recipients Blood collection kits will be sent to study participants and returned to a central biorepository. To reduce waste from kits which are not returned, only enrollees who participate in follow-up surveys will be sent these materials.

Choice of Blood as Biospecimen Saliva, blood, and surgical tissue were all considered as potential biospecimen sources in the design of the IDDB. Blood represents the best single compromise based on the following considerations. *Biospecimen value:* neither saliva nor surgical specimens provide circulating biomarkers; blood provides quantitatively better DNA than saliva. *Logistics*: saliva is easier to collect, but because Dupuytren patients are likely to be seniors who

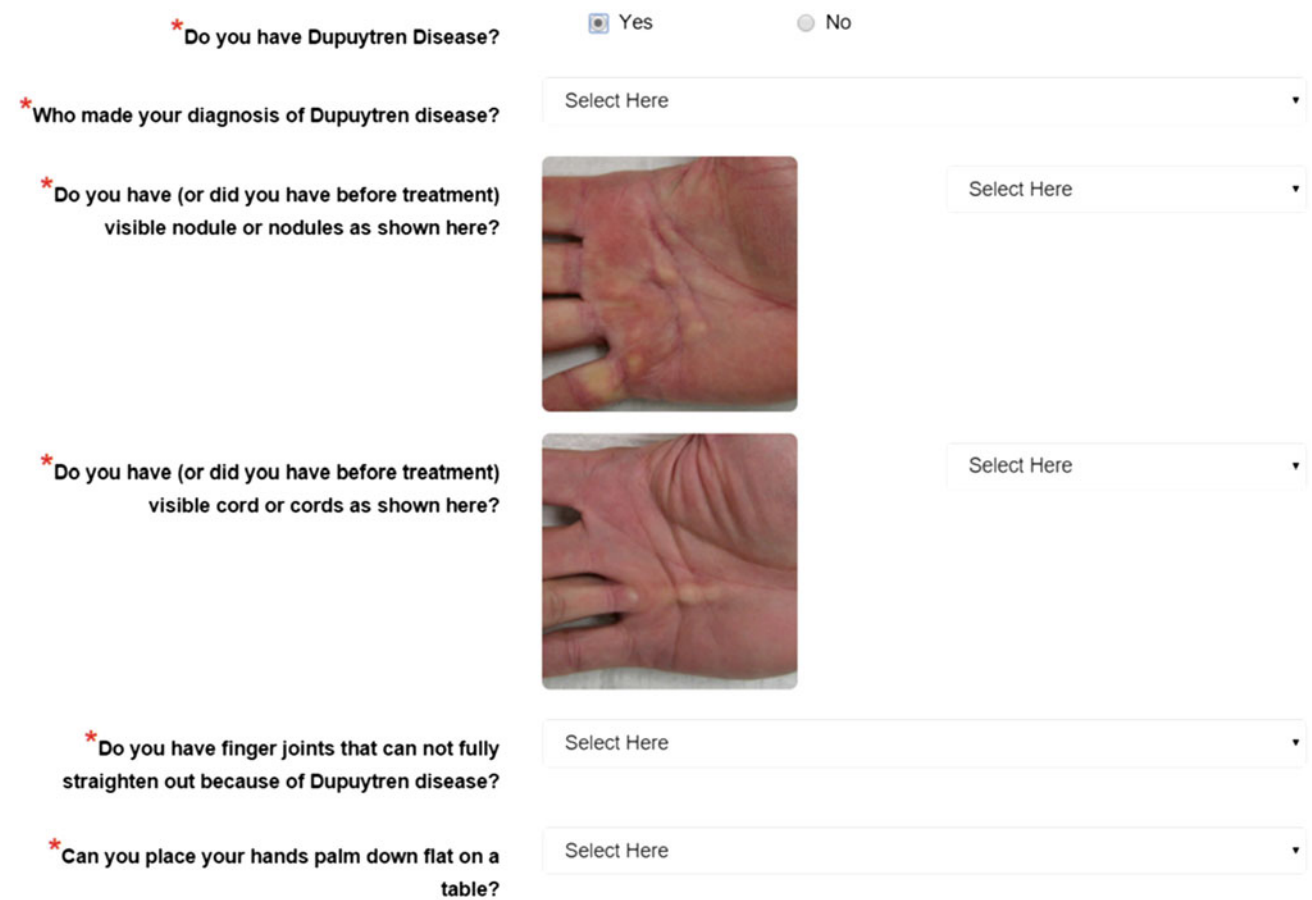

Fig. 56.1 Self-diagnosis form (this screen capture from the IDDB enrollment form shows the self-diagnosis tool and follows the model of a validated self-diagnosis tool (Pervulesko et al. 2011))

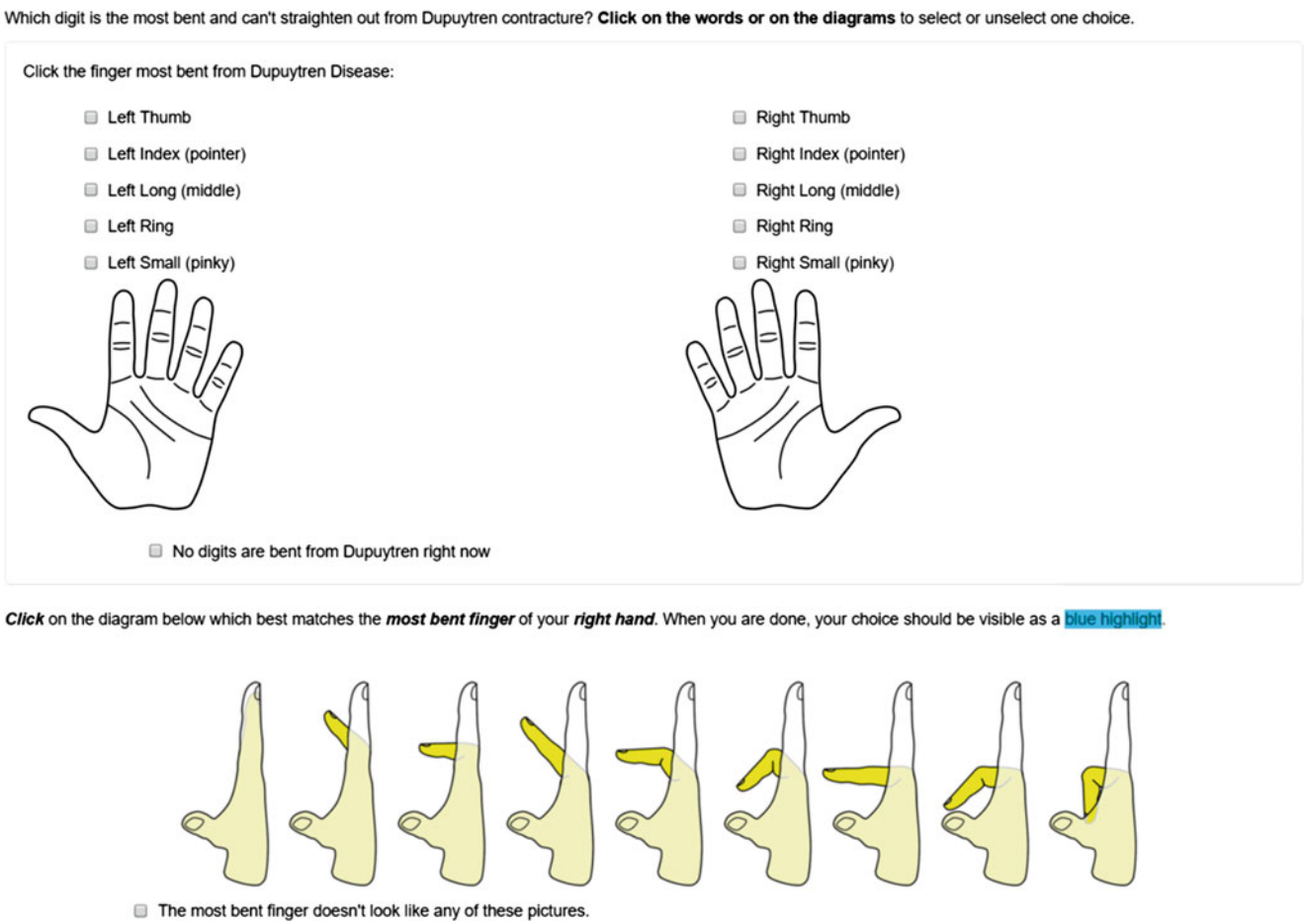

Fig. 56.2 Form for self-documentation of deformity (this screen capture from the IDDB enrollment form shows the deformity severity tool based on a validated self-reported tool (Dias and Braybrooke 2006))

have annual physical examinations, blood can be collected at that time; surgical tissue specimens require both third-party involvement and an open procedure. *Cost:* saliva is less expensive, surgical tissue specimens more expensive than blood.

56.2.3.3 Phase 3: Analysis to Identify Biomarkers

Once an adequate sample size of biospecimens is collected, the biorepository samples will be analyzed for DNA and other biomarkers and correlated with clinical severity data to identify biomarkers of severe Dupuytren Disease. Biorepository sample materials, biorepository analysis results, and clinical data will be made available to other researchers using open-access guidelines.

56.2.3.4 Simultaneous Pilot Study

From both a practical and cost perspective, phase 1 had to be fully operational before going live. Phase 1 form design and database construction completed many iterations and cycles of beta testing prior to launch. Phases 2 and 3 present a different set of challenges and costs. For this reason, small pilot versions of phases 2 and 3 will be run to identify unanticipated costs and logistic obstacles prior to the full launch of phase 2. Pilot study information will also provide information for grant applications to fund phases 2 and 3. A pilot study of phases 2 and 3 involving 100 patients will be launched after the first 100 enrollees completed the first follow-up survey.

56.2.4 Staff and Partner Organizations

The IDDB is an original program designed, conducted, and sponsored by the Dupuytren Foundation. *Phase 1* online form and secure database architecture have been developed in collaboration with the nonprofit Arthritis Research Foundation (https://www.arthritis-research.org/), the International Dupuytren Society (http://www.dupuytren-online.info/), and input from individual Dupuytren surgeons across the globe. Statistical analysis of de-identified survey data with Stata software (http://www.stata.com/). *Phase 2* sample collection and biorepository development will be in collaboration with a central biorepository such as the Mayo Clinic Biobank (http://www.mayo.edu/research/centers-programs/mayo-clinic-biobank/overview). *Phase 3* testing and analysis will be conducted in collaboration with the UCLA Department of Human Genetics (https://www.genetics.ucla.edu/). In addition, de-identified survey and biorepository resources will be shared with other global Dupuytren researchers using open-access guidelines.

56.2.5 Do List

The IDDB has a flexible design, allowing for incremental improvement along the way. A number of additional features are under development, including the following.

56.2.5.1 Phase 1: Smartphone Goniometer App

Range-of-motion measurements pose significant hurdles, including dynamic contractures and technical difficulties with self-documentation. The rate of contracture progression over time is an important index of disease aggressiveness, which has not been adequately documented in prior studies on a large scale. The IDDB is developing a smartphone app to collect goniometric documentation based on hand images obtained using only a smartphone camera. The goal is to collect standardized measurement data without requiring a visit to a therapist or physician.

56.2.5.2 Phase 2: Cost-Effective Blood Collection

Costs and logistics of mailing, receiving, and storing blood samples of more than 10,000 patients are daunting. Further work is needed with the Mayo Biobank program to streamline this process and to create a mechanism through which that researchers outside the IDDB will have open access to the biorepository.

56.2.5.3 Phase 3: Distributed Computing for Biomarker Analysis

DNA analysis on this scale requires enormous computing power. Such power may be provided by the collaborative work of multiple computers, referred to as distributed computing or open grid computing. This is a rapidly changing technology and will be revisited as the IDDB progresses.

56.2.6 Funding

The IDDB is funded by the nonprofit Dupuytren Foundation, which has been supported by individual contributions. The budget for the entire IDDB project is projected to be $5,000,000, which is beyond the expectations for individual funding. The Dupuytren Foundation is currently seeking funding sources from family foundation and corporate grants.

56.3 Additional Benefits

Dupuytren Disease is not simply a problem that affects the hands. It is a systemic disorder associated with Ledderhose Disease, frozen shoulder, and possibly Peyronie disease. In addition, patients with Dupuytren Disease have greater incidence of a variety of malignancies and greater risk of early death, only part of which is explained by increased cancer risk (Gudmundsson et al. 2002; Macaulay et al. 2012; Mikkelsen et al. 1999; Wilbrand et al. 2000, 2002, 2005). Effective medical treatment could impact longevity and reduce cancer risk in addition to improving quality of life. Beyond this, the parallels of Dupuytren myofibroblast-related fibrotic biology with life-threatening fibrotic conditions such as arteriosclerosis, cirrhosis, renal interstitial fibrosis, and pulmonary fibrosis suggest that better treatment of Dupuytren biology could advance treatment options for a wide range of non-Dupuytren disorders. The IDDB is the only existing Dupuytren research program, which *may lead to health benefits well beyond the scope of hand deformity*.

56.4 Summary

Historically, Dupuytren research has focused on the anatomy, biology, and treatment of Dupuytren *contracture* deformity, the complication of Dupuytren Disease. For most Dupuytren patients, *progress in the management of Dupuytren biology has remained stagnant* for the duration of their lives. The International Dupuytren Data Bank is an independent research project that seeks to change this. The IDDB uses crowdsourcing, new web technology, and open-access research to search for the cause and the cure of Dupuytren Disease.

Conflict of Interest Statement The author has no conflicts of interest to declare.

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International Clinical Research – The Australian Perspective: A Personal View

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Stephen G. Coleman

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57.1 Introduction

Australia is a long way from everywhere, which makes large database research difficult. Australia has a population of approximately 25 million, and as the country was populated by European migration around 200 years ago, the majority of the current population is of European ancestry. There is thus a high incidence of Dupuytren Disease. The nearest continents to Australia are Asia and Antarctica, neither of which has a very high incidence of Dupuytren patients within them. In order to conduct any research of significance into Dupuytren Disease it will require an association with larger population groups.

In 2006, offers were made from Auxilium Pharmaceuticals to participate in multicentre international trials on research with collagenase treatment for Dupuytren Disease. I have continued with Dupuytren Disease research since that time.

57.2 Advantages and Disadvantages

To participate in any international study will depend on the study group and the population to be investigated. One needs to select the population group carefully. For example, Dupuytren Disease is rare in Asia, so that population group may not be suitable. Melanoma is common in tropical Australia, but much rarer in a northern

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European nation. If an association with an international group or country is to be considered, the relative incidence of the disease to be investigated should be considered.

With international involvement, case numbers multiply, enabling a large series to be investigated. For example, in one multinational study over a 5-year period, it was possible to follow up 950 Dupuytren subjects injected with collagenase in 1081 treated joints.

By working in differing countries, a variation in population subjects can be expected. This may reduce genetic/country/external influences and give a more balanced population study group. The cost can be spread by working in differing countries. Industries, research foundations and charities have different rules in varying countries which may allow more opportunities.

The type of research study needs to be carefully considered. Data collection is relatively straightforward, but tissue collection may be difficult if it requires transfer from one country to another, especially if refrigeration/liquid nitrogen is required. The cost may become prohibitive. Blood, urine or tissue samples are difficult to transport internationally. There is a risk of sample loss over such large distances. Customs may block the import of human tissues or fluids and needs to be confirmed before international transfers. Monitoring of surgical techniques may not be comparable between countries.

A major advantage of the digital age is that it has made the world smaller. Although Australia is on the opposite side of the world to Europe and the Americas, it is readily accessible via the Internet. Facilities such as Skype may allow videoconferencing, and electronic case report forms (eCRF) make transfer of information and data simpler and instant. Teleconferencing is a possibility, although additional costs may result.

57.3 Considerations: Protocols

All participating clinicians will be required to follow the same strict procedures/protocols. Without that, comparison of intercountry results will not be possible. Participants may be required to attend a training course in a single country. At the beginning of the CORD 1 and CORD 2 collagenase studies, it was necessary to travel from Australia to the United States for 2 days, to attend a pretrial training course. This required over 20 h flying in each direction. When the first collagenase multi-cord concept trial was conducted in Brisbane, Australia, in 2010, representatives from Auxilium flew from the United Kingdom and the United States to Australia to assess the physical outcome on patients of doubling the drug dose with this pioneer trial.

The aim of a clinical trial may vary in differing countries. Collagenase, for example, has differing levels of acceptance and indications in the United States, Europe, Australia and Asia. Country expectations on outcomes for regulatory authorities, social outcomes, quality of life and employment differ. The bar may be lower or higher in some countries. Complication implications may also vary. One should ensure there are no legal concerns if complications arise. There may also be differing expectations with industry versus investigative trials.

57.4 Considerations: Trial Conduct

All clinical trials must follow the World Medical Association (WMA) Declaration of Helsinki which was initiated in 1964. This was adopted by the 18th WMA General Assembly in Helsinki, Finland, in June 1964. The WMA has developed this Declaration as a statement of the ethical principles for all medical research involving human subjects, including research on identifiable human material and data.

Thirty-five principles are to be followed. The primary principle is that the physician's duty is "to protect the patient's health". This takes precedent over all other interests. Trials must be conducted by qualified professionals, and all subjects must have informed consent with the indications for the trial, the conduct of the trial and any complications that may arise.

Clinical research must be ethical, monitored and be directed at assessing efficacy, progression,

safety and complications of both the procedures and/or medications involved in the trial and the disease itself. Human research requires ethical review. Ethics may vary between countries and need careful consideration.

All clinicians must follow good clinical practice (GCP). To conduct the trial, the participants must use and gain approval from a human research ethics committee (HREC). The HREC will ensure strict ethics compliance, and by using a HREC faster, ethics approval may be possible. The HREC will ensure that all participants, both medical staff and patients, are provided with strict informed consent explaining the risks, benefits, sponsors, funding and general information. All adverse events (AEs) and serious adverse events (SAEs) must be strictly recorded and reported. Participants must sign a non-disclosure confidentiality clause.

I would recommend that any international trial be conducted under the supervision of a contract research organisation (CRO). Most countries will have a local CRO, but one must ensure the CRO has international accreditation. The CRO will provide clinical trial support and coordination and assist with recruitment, documentation and planning of the trial. The CRO will be your constant companion throughout the trial. They regularly monitor data and that you as the principal investigator are up to date with all data recording and protocol adherence. They will assist in auditing and ensure every data recording is consistent and signed. All records must be accurate. As the research saying goes "if it isn't written down, it didn't happen". The other important saying is "if it isn't written down correctly, it didn't happen either".

Data collection is time-consuming and a difficult process requiring close attention to detail. The CRO will have centralised facilities for statistical analysis and can communicate readily with the parent international organisation if necessary. One also must ensure that all data are retained for up to 5 years, which again becomes the responsibility of the CRO which has facilities to do so. If drugs are involved, it is necessary to have a CRO involved as they will be aware of the pitfalls and regulations for drug management in trials.

57.5 Considerations: Investigator Options

I strongly suggest there is a single organiser in the primary country for the international trial. A single person should take primary responsibility for writing the protocols and rules and to coordinate the results. This obviously can be with the assistance of a committee or other nominated staff. A strict and detailed protocol must be provided to all participants. The definitions of the inclusions or exclusions of patients should be clarified. Decisions regarding results and defining patient participation such as with randomisation ratios should be decided by the primary coordinator. An example in the AUX CC861 multi-injection trial involved only 20 subjects, but there were 85 pages of protocol to define the trial.

A principal investigator should be nominated for each international site. They are under the control of the primary organiser noted above. Each principal investigator should be the primary contact for all communications and take responsibility for the conduct of the trial. The principal investigator must confirm consent forms and any other literature are signed. The principal investigator at each site is responsible for adherence to all protocols. The principal investigator will be the prime contact for the CRO. As noted earlier, the principal investigator may need to travel or attend teleconferences or training meetings. Generally, each site principal investigator will become one of the primary authors of publications.

57.6 Summary

All the above must be considered before one agrees to participate in an international trial. I do, however, strongly recommend participating in international clinical trials if you are given the opportunity. It will be a challenge and strict rules need to be followed. It will take a considerable amount of your time, and many difficult decisions will require your attention.

The main advantage is that it will broaden the clinical possibilities for trials and data collection.

You may be part of a group that can prove or disprove new treatments. There is no doubt it will broaden your experience, and you will meet and make new international colleagues. It is also likely to increase your international status and enable attendance and presentations at future international meetings and lead to publications in world standard publications. Accept any offers with enthusiasm, but with the above important considerations. Dupuytren Disease is an international condition which requires international research to develop a "cure".

Conflict of Interest No conflict of interest. The author has been involved in Collagenase research since 2006 with Auxilium Pharmaceuticals. The author has received investigator research funding and is currently on the advisory board to Actelion Pharmaceuticals in Australia.

Related International Trials

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Open Questions and Potential Answers

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As of this writing, Dupuytren questions far outnumber answers.

58.1 What *Is* Dupuytren Disease?

Is it one disease or several similar appearing conditions? Is it a discrete disease, or simply part of the spectrum of the biology of aging, along with gray hair, smile lines, and loss of hearing? Or is it exactly the opposite, a failure of aging, a failure of cell senescence? Normal fibroblasts divide about 60 times before becoming senescent. Do Dupuytren myofibroblasts simply fail to age and die gracefully? Are Dupuytren, Ledderhose, knuckle pads, frozen shoulder, and Peyronie disease imposters, or cousins, or clones? Why does this disease develop in the hand and not in the thigh or earlobe? In the pursuit of understanding Dupuytren biology, is it helpful or is it misleading to use data from other localized fibroses such as desmoid tumor, keloid, or hypertrophic burn scar? Is it helpful or is it misleading to use data from more generalized fibroses such as cirrhosis, pulmonary fibrosis, scleroderma, or arteriosclerosis? Could Dupuytren be a protein-folding disease? How could that question be answered? Where does collagen lie on the line between cause and consequence?

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58.2 What *Accompanies* Dupuytren Disease?

It's not a simple tally. Dupuytren research has spawned answers for questions which do not yet exist – data, factoids, and anecdotal observations which beg the question "what does this mean?" It's not surprising that Dupuytren Disease has been found to be associated with abnormalities in the collagen metabolism arena: autoantibodies to type 1 collagen and elastin (Menzel et al. 1994), abnormal levels and ratios of matrix metalloproteinase-2, matrix metalloproteinase-14, tissue inhibitor of metalloproteinase-14 (Wilkinson et al. 2012), and circulating fibrocyte levels (Iqbal et al. 2014). What remain unexplained are associations of seemingly unrelated issues and Dupuytren Disease. What is the molecular relationship of Dupuytren Disease to diabetes (Noble et al. 1984)? To hyperlipidemia (Sanderson et al. 1992)? To having a low body mass index (Gudmundsson et al. 2000)? To sympathetic dystrophy (Dickson 1964)? To hypothyroidism (Macaulay et al. 2012)? To depression (Macaulay et al. 2012)? To early mortality (Gudmundsson et al. 2002)? To cancer risk (Gudmundsson et al. 2002)? To psoriasis (Patel et al. 2014)? To Caucasian heritage? To tissue iron deposits (Berg et al. 1972)? To the Charlson comorbidity index (Macaulay et al. 2012)? HLA type (McCarty et al. 2010)? IgA immune complexes (Houghton et al. 1983)? DR+ T cells and CD5+ B cells (Gudmundsson et al. 1998)? *All* of these associations have been reported; *almost none* have received the type of in-depth additional investigation needed to confirm, refute, or make sense out of the finding.

58.3 What Do Dupuytren Patients Want?

More importantly, what do they *not* want? Dupuytren patients *don't* want to be told that they have an incurable disease. They *don't* want to be rushed through a surgical evaluation because their hands are not "bad enough yet." They *don't* want their research into alternative treatments dismissed without discussion. They *don't* want to be told and told that there is nothing that they can do. They *don't* want to be treated by specialists who tell them that theirs is the only successful treatment or who are not familiar with other treatment options or who can't provide expertise on possibly associated diseases. Dupuytren patients want what *all* people want: respect, hope, empowerment, and complete, objective information. These are things that we can and should provide, even as the search for a cure continues.

58.4 Why Is There a Patient-Driven Movement Pushing for Better Dupuytren Treatments?

People, in general, are risk averse and aren't comfortable unless potential benefits greatly outweigh potential risks (Kahneman and Tversky 1979). This creates a problem for Dupuytren patients, because current Dupuytren treatment doesn't fit that model: the most common treatment (fasciectomy) offers temporary gains with moderate risk of prolonged recovery and moderate risk of permanent complications. It's no surprise that patients are so willing to embrace treatments which provide even shorter projected periods of improvement (collagenase, needle fasciotomy) or are discouraged by some surgeons despite promising benefits (radiotherapy), because these approaches have much less perceived risk than fasciectomy. The motivation is that people don't like what their doctor recommends for their Dupuytren Disease. They come home from the doctor's office and reach out online with the thought that there *must* be something better.

58.5 What Is Really Going on with Dupuytren Care?

The long-term outcome of Dupuytren treatment has not changed in decades despite many flurries of activity in the technical treatment of Dupuytren contracture deformity. We must recognize that

we have reached an impasse, an invisible wall which must be breached. The invisible wall is the misperception that Dupuytren Disease is a hand condition, that contracture is the disease and not the end result of the disease, and that procedures for contracture are the only option. As long as these misconceptions persist, a cure for Dupuytren Disease will remain out of reach.

58.6 How Does One Approach a Traditionally Insoluble Problem?

Move things around!. That's the advice I received as a child when I complained that I couldn't find what I was looking for in my messy bedroom. Dupuytren Disease is the same: we can't find what we are looking for because we mistake obstacles for boundaries. At the same time, we see things that aren't there: we confuse change for progress, anecdote for insight, wishful thinking for strategy, good luck for success, and tradition for understanding. This must stop. It's time to move things around, to solve what only *appears* to be an insoluble problem. We can use three strategies: examine failure, question convention, and engage outsiders.

- *Examine failure*. What are some of the failures of Dupuytren care? So far, we have failed to provide a permanent solution. We have failed to develop an objective, predictive measure of Dupuytren Disease severity. We continue to fail to provide patients an acceptable set of treatment choices. We fail to grasp the number of people with Dupuytren Disease who are undocumented, or who are unhappy with the results of their treatment, or who avoid any treatment evaluation because they have heard stories of unhappy Dupuytren treatment outcomes. We (hand surgeons) have overestimated the happiness our Dupuytren patients have with their outcomes. We need to keep these issues in our view: they are the most obvious areas which need improvement.
- *Question convention*. Does it make sense to accept a high-morbidity procedure with unpredictable outcome and limited duration of control as the standard of care for a benign, painless disorder? Does it make sense to ignore all aspects of an inherited systemic connective tissue disorder other than the late effects it has on the palms and fingers? Does it make sense to evaluate treatment effectiveness of an ongoing chronic progressive disease by lumping together outcomes evaluated at a wide range of follow-up durations after treatment as if recurrence rates were linear and uniform? Does it make sense to evaluate overall treatment effectiveness based on selected outcomes segregated by posttreatment criteria? None of these make sense if the goal is what is the best interest of the patient. We should question on how these flawed approaches became acceptable standards and work to correct these flaws.
- *Engage outsiders*. If the cure for Dupuytren Disease could be found in a local procedure, it would exist. Instead, there are a great number of procedural variations which address only a small aspect of Dupuytren Disease and provide nearly identical outcomes. Further progress is unlikely unless investigation broadens to address aspects of Dupuytren Disease other than deformity. Vascular surgery evolved dramatically with new surgical approaches, but real progress in outcomes came from better understanding of disease risk factors, biomarkers, and systemic interventions. The same is true for rheumatoid arthritis, peptic ulcer disease, and most bacterial diseases. Surgeons must escape their Dupuytren procedure-centered tunnel vision and engage their rheumatology, gerontology, cell biology, and genetic colleagues to take on the challenge.

58.7 Why Aren't More People Doing Dupuytren Research?

Why do people do medical research in the first place? Curiosity isn't enough. Profit, fame, self-interest, and altruism all factor in, but ultimately, it is a matter of time and money. Dupuytren Disease is not a good fit for practice-based

surgical registry research. Surgeons, in general, are busy. Compared to patients with other common non-emergent benign hand conditions such as tendinitis, neuritis, or arthritis, care of Dupuytren patients tends to be labor-intensive relative to reimbursement. This discourages surgeons from developing a Dupuytren focus to their practice, a disincentive to participating in a surgical registry. At the same time, funding drives research, and research funds are scant for what is perceived to be an uncommon benign nuisance experienced only by seniors.

58.8 What Needs to Be Done?

We need to raise awareness of Dupuytren Disease, its health implications and potential impact of effective Dupuytren medication on other fibrotic disorders. By doing so, Dupuytren research funding can be increased, and a greater number of researchers can be recruited to study the disease. We need to leverage the efforts of Dupuytren patients to raise awareness by social media and by direct engagement with their politicians to increase government funding of Dupuytren research. We need to keep reminding ourselves that the only reason that there is not yet a cure for Dupuytren Disease is that no one has yet put the pieces together on the necessary scale to achieve the task. What needs to be done is to plan in reverse: assume that a cure is possible and then outline the steps needed to develop a cure. This is the basis of the International Dupuytren Data Bank, discussed elsewhere in this text (Eaton 2016).

And finally, *why is there not a poem about Dupuytren Disease?*

Well, now there is.

Dupuytren Disease

Just Dupuytren. Though hard to say in fluent French, your name became an eponym, your curse cliché for fingers bent, coerced to clench, the wrench you throw into the hand, intention no one understands, entrenched, you never go away.

How Dupuytren, to classify your lumps and cords, skin gone awry, the strings of joints curved out of line turn fingertips to pointed swords to score the face when washing up. You pour the palm into a cup. Disorder, strange and undefined.

Your Dupuytren biology lies in the guise of normalcy, yet collagens, T-I-M-Ps and MMPs somehow devise a plot with myofibroblasts to modify their mien en masse to what and when? A mystery.

The Dupuytren inebrium – your lid's ajar, you're out of plumb, near or far, where are you from, just scar disequilibrium? You hide inside a next of kin, not diet nor a vitamin, but in the lines of dad and mum.

Oh, Dupuytren, you fight defeat, by any means, you're hard to treat. Surgery, so incomplete, cannot delete your secret genes resisting pharmacology, persisting after therapy, existing only to repeat.

Now, Dupuytren. You need a cure for everyone who must endure and dynasties yet immature. Yes, you can hide, but you can't run: We'll learn your scheme like Aristotle, put your genies in a bottle, lay to rest your nom de guerre. Yes, Dupuytren. You need a cure.

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