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Focused extracorporeal shockwave therapy in Dupuytren's disease – A hypothesis

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ABSTRACT

Dupuytren's disease is a progressive disease due to unknown causal agents or genetics. An epidemiological analysis of 566 cases in North Germany estimated that around 1.9 million Germans are suffering from Dupuytren's disease. Beside Dupuytren's disease, there are a number of further less common forms of progressive fibromatosis, such as knuckle pads, plantar fibromatosis or Peyronie's disease. Surgery in plantar fasciectomy yields to a 60% recurrence rate depending on the extent of the plantar fasciectomy. Peyronie's disease of the penis affects middle-aged men between 40 and 60 years with penile pain, curvature during erection and potential erectile dysfunction. In a clinical randomized-controlled trial in Peyronie's disease 2000 focused extracorporeal shock waves reduced pain significantly and improved erectile function and quality of life. We hypothesize that focused extracorporeal shock wave therapy is able to reduce Dupuytren's contracture, a fibromatosis of the palm and improve function. Given the fact that recurrence rate in Dupuytren's disease is high und unpredictable extracorporeal shockwave therapy as a non-invasive tool might be applicable both, in primary and secondary prevention of the progression as well as for treatment. As such we have planned a randomized-controlled trial (ClinicialTrials.gov, NCT01184586) studying the effect of high-energy focused extracorporeal shockwave therapy on patients suffering Dupuytren's disease with patient-related outcome measures such as the DASH score and the Michigan Hand Outcome Questionnaire (MHQ) as primary outcome parameters.

Introduction/Background

Dupuytren's disease is a progressive disease due to unknown causal agents or genetics. An epidemiological analysis of 566 cases in North Germany estimated that around 1.9 million Germans are suffering from Dupuytren's disease [1]. Dupuytren's disease contains nodules and cords in the fascia as the epicenter of disease progression. Nodules contain whorls of collagen bundles and are densely packed with contractile fibroblasts and myofibroblasts. These highly contractile cells are linked to the fascia matrix through transmembrane integrin receptors. The cytoplasmic tail domains of the alpha beta integrin receptors provide a structural link between extracellular matrix (ECM) and the actomyosin cytoskeleton. Depending on the degree of the flexion contracture in Dupuytren's disease, various therapeutic options are available to date. Surgery is often the mainstay in progressive Dupuytren's disease with either selective or total aponeurectomy. However, these operations are not free from complications and still bear the risk of recurrences.

Non-invasive options include percutanous fasciotomy or collagenase injection. The latter has been tested in a randomized-controlled trial published in the New England Journal of Medicine with 308 patients enrolled (NCT00528606) [2]. Collagenase clostridium histolyticum significantly reduced contractures and improved the range of motion in joints affected by advanced Dupuytren's disease. In the long-term the cords at the level of the PIP joint appear to more recurrent than at the MP joint after collagenase injection with an 8 years follow-up [3].

In early stage Dupuytren's contracture, radiotherapy has been suggested to limit disease progression. A cohort study of 135 patients with 208 hands involved received orthovoltage radiotherapy (120 kV, 20 mA) with a total dose of 30 Gy separated by a 6–8 weeks interval [4]. After a follow-up of 13 years nodules and cords remained stable in 59%, improved in 10% and progressed in 31%.

Medical antifibrotic agents inhibiting TGF-beta such as *N*-acetyl-L-cystein (NAC) and angiotensin-converting enzyme (ACE) inhibitors have been suggested [5] to be able to limit the progressive disease; however, no prospective clinical data are available currently in this regard. ACE inhibitors appear to limit fibrosis such as in muscle regeneration following injury [6] or limits capsular contracture around silicone implants in plastic surgery [7].

Beside Dupuytren's disease, there are a number of further less common forms of progressive fibromatosis. Knuckle pads are often related to palmar keratoderma, and hand eczema appear on the extensor side of the long fingers especially over the metacarpophalangeal (MP) and proximal interphalangeal joints (PIP) [8,9]. There

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a rare inherited skin disease such as epidermolytic plamoplantar keratoderma Vörner-type where thickening of the palms and soles are associated with knuckle pads based on keratin K9 mutations [10].

Plantar fibromatosis, also known as Ledderhose disease [11,12], is not seldom associated with Dupuytren's disease of the palms especially among diabetic patients [13]. Surgery with plantar fasciectomy yields to a 60% recurrence rate [14]. While local resection had a 100% recurrence rate in Ledderhose disease, total plantar fasciectomy achieved a 255 recurrence rate. Peyronie disease at the penis affects middle-aged men between 40 and 60 years with penile pain, curvature during erection and potential erectile dysfunction. As in the case of early Dupuytren's disease of the palm, radiotherapy has been applied in uncontrolled trials [15].

Notably, extracorporeal shockwave therapy has been discussed in Peyronie's disease. In an animal model for Peyronie's disease 2000 shockwaves were applied [16]. In a clinical randomized-controlled trial in Peyronie's disease 2000 focused shock waves reduced pain significantly and improved erectile function and quality of life [17]. About half of the patients in one series of 44 patients had a significant reduction in angulation following shockwave therapy [18].

Hypothesis

Focused extracorporeal shock wave therapy is able to reduce Dupuytren's contracture and improve function. Given the fact that recurrence rate in Dupuytren's disease is high and unpredictable extracorporeal shockwave therapy as a non-invasive tool might be applicable both in primary and secondary prevention of the progression as well as for treatment.

Evaluation of the idea

A randomized-controlled trial would be at best determine the effects of focused extracorporeal shockwave therapy in Dupuytren's disease. We have planned such a two-arm RCT comparing high energy focused extracorporeal shockwave therapy (ESWT, Storz Duolith) with 3 weekly sessions with 1000 impulses 0.6–0.8 mJ/mm^2 each. This RCT is registered at ClincialTrials.gov under the number NCT01184586.

The control group should receive sham extracorporeal shock wave therapy with a similar impulse rate (1000 impulses), however, low to nil energy (0.01 mJ/mm^2) to enable blinding of the patient. We will use a sealed shockwave probe in the sham ESWT group which is similar to the usual probe but has a shield to block the shockwaves inside the probe. The probe is mounted depending on the result of the randomization process from an independent third person, thus the examiners as well as the patient and shockwave physician are blinded to the group allocation. Extracorporeal shockwave therapy is associated with a given sound of each applied impulse and thus, it is necessary to apply sham impulses of low energy or a modification in the transducer in order to obtain sham extracorporeal shock wave therapy.

As far as primary outcome measure is concerned patient-related scores, range of motion and grip strength might be considered. We would prefer a patient-related score to study the efficacy of extracorporeal shockwave therapy in patients suffering from Dupuytren's disease rather than range of motion measurements. We believe that the daily limitation of Dupuytren's disease in activities of daily living is much more relevant than for example a 10° gain in finger extension. As such, validated outcome measures are needed in this regard. To date there are no Dupuytren-specific outcome questionnaires validated in the literature.

Table 1
Reported DASH scores at baseline and after surgical or non-surgical interventions in Dupuytren's disease.

Authors	N	Intervention	Mean DASH ± SD	Range
Degreef et al. (2009)	80	Baseline	15	0–69
Atroshi et al. (2006) [21]			24	
Skoff, 2004 [22]			37	
Zyluk and Jagielski (2007) [23]	54	Selective aponeurectomy	54 vs. 32 (12 months)	
Ganeval et al. (2010) [24]	20	Fasciotomy	Postop Quick-DASH 20	0–73
Johnston et al. (2008) [25]	19	Brunner incisions, selective aponeurectomy	24 ± 20 vs. 15 ± 12 (3 months) vs. 8 ± 8 (14 months)	
Herweijer et al. (2007) [26]	46	Selective aponeurectomy	12 ± 13 vs. 7 ± 9 (10 months)	
Högemann et al. (2009) [27]	61	Total aponeurectomy	7	0–33

Table 2
Reported Michigan Hand Questionnaire (MHQ) scores at baseline and after surgical or non-surgical interventions in Dupuytren's disease.

Authors	N	Intervention	Mean MHQ
Johnston et al., 2008	19	Brunner incisions, selective aponeurectomy	58 ± 16 vs. 75 ± 16 (3 months) vs. 87 ± 12 (14 months)
Herweijer et al., 2007	46	Selective aponeurectomy	75 ± 13 vs. 84 ± 15

We would choose the Disabilities of Arm Shoulder and Hand Questionnaire (DASH) as **primary outcome measure** as a self-reported questionnaire for hand function and disability. The DASH is a 30-items patient-reported questionnaire with two adjuncts, DASH-Sport (4-items) and DASH-Work (4-items), which will be evaluated, too.

Notably, the validation of the aforementioned DASH score included patients suffering from Dupuytren's disease. Longitudinal construct validity has been assessed in patients including those with Dupuytren's disease and the responsiveness is moderate (effect size 0,5). The DASH questionnaire has a good validity with the subscale of SF-36 [19]. The test–retest reliability of the DASH questionnaire has been found to be excellent (ICC = 0.96) [20]. The DASH score has been used in eight clinical trials to date (Table 1).

Another validated patient-related outcome score is the *Michigan Hand Outcome Questionnaire* (MHQ). The MHQ [28] is a side-specific questionnaire with 25 unilateral and 12 bilateral questions, including hand function, work performance, and cosmetic appearance. It generates a score from 0 (poor) to 100 (no disability at all). The MHQ is responsive to clinical change [29] and has been applied in two clinical trials yet (Table 2).

Current and potential future clinical applications of extracorporeal shockwave therapy

Currently, extracorporeal shock wave therapy is used in urology to treat stone disease [30], erectile dysfunction [31], and chronic pelvic pain [32]. In orthopaedic surgery, especially tendon disorders at the Achilles tendon [33], patella tendon [34,35] or calcifying tendonitis of the shoulder [36] and tennis elbow tendinopathy [37] as well as for bony non-unions [38]. In burn surgery, extracorporeal shockwave therapy has been used in non-randomized trials demonstrating wound healing capacity [39,40]. Similar effects

have been reported using extracorporeal shock wave therapy in the treatment of neuropathic ulcers [41]. Given the aforementioned effects of extracorporeal shockwave therapy in Peyronie's disease, a fibromatosis of the penis, one might suspect, as we have hypothesized, that the same extracorporeal shock wave therapy might be a valuable tool in treating Dupuytren's disease, a fibromatosis of the palm.

Consequences of the hypothesis and discussion

Given the similar nature of the aforementioned progressive fibroproliferative diseases, besides, extracorporeal shockwave therapy might be applicable for plantar fascia (Morbus Ledderhose), or the dorsal proximal interphalangeal and metacarpophalangeal joints (knuckle pads), which might be treated in analogy to the Dupuytren's disease. However, randomized-controlled studies have to elucidate on the effect of extracorporeal shockwave therapy in fibroproliferative disorders, the optimal timing and dosage, as well as recurrence rates in the long-term perspective.

Conflict of interest

No author has anything to disclose. We did not receive any internal or external funding.

Disclosure

We have nothing to disclose. We received no internal or external funding.

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