doi: 10.2490/prm.20210023 Progress in Rehabilitation Medicine 2021; Vol. 6, 20210023

ORIGINAL ARTICLE

Collagenase *Clostridium histolyticum* Injection Therapy Improves Health-related Quality of Life in Patients with Dupuytren's Disease

Takuro Kuboi, MD [a] Tsuyoshi Tajika, MD, PhD [b] Fumitaka Endo, MD [a] Wataru Goto, MD [c] Ichiro Nakajima, MD [c] Satoshi Hasegawa, MD [c] Daisuke Nakajima, MD, PhD [d] Takafumi Hosokawa, MD [e] and Hirotaka Chikuda, MD, PhD [a]

Objectives: This study was conducted to investigate the changes in clinical and psychosocial outcomes in patients with Dupuytren's disease after initial treatment with collagenase *Clostridium histolyticum* (CCH) injection. **Methods:** This study involved 14 patients with Dupuytren's disease who underwent treatment with CCH injection. The range of motion of each phalangeal joint was measured before treatment and at 6 months posttreatment. The following assessments were also carried out pre- and posttreatment: the Geriatric Depression Scale Short – Japanese version (GDS-J) to evaluate depressive status, Hand 10 to assess hand health status, and EuroQol-5-dimension-3-level Japanese version to evaluate health-related quality of life **Results:** Significant improvements were found in metacarpophalangeal joint extension and proximal interphalangeal joint extension. Significant differences were also found between values before the initiation of CCH injection and those at 6 months posttreatment for the EuroQol index score and the EuroQol Visual Analog Scale (VAS). Significant positive correlations were found between the pre- to posttreatment change in GDS-J scores and for the change in Hand 10 scores. Moreover, a significant negative correlation was found between the change in GDS-J scores and change in EuroQol index scores/EuroQol VAS scores before and at 6 months after CCH injection. **Conclusions:** For patients with Dupuytren's disease, CCH therapy directly improved the health-related quality of life. The degree of improvement of depressive status was associated with the degree of improvement of hand health status and health-related quality of life.

Key Words: collagenase; depression; Dupuytren's disease; EuroQOL patient-reported outcomes

INTRODUCTION

Dupuytren's disease is a fibroproliferative disease that produces fixed finger flexion contractures that are progressive and irreversible.[1)] Quality of life (QOL) is reduced because of disabling limitations in performing activities of daily life such as body washing, putting on gloves, shaking hands, and doing handicraft.[2)] Our previous study demonstrated an estimated prevalence of Dupuytren's disease of 7% in Japan.[3)] To treat Dupuytren's disease, fasciectomy or fasciotomy has been performed in Japan. Furthermore, between 2012 and 2014, Hirata et al. investigated the efficacy and safety of collagenase *Clostridium histolyticum* (CCH) injection to treat Dupuytren's disease and revealed good outcomes similar to

Received: March 9, 2021, Accepted: May 12, 2021, Published online: May 26, 2021
[a] Department of Orthopaedic Surgery, Gunma University Graduate School of Medicine, Maebashi, Japan
[b] Department of Rehabilitation, Gunma University Graduate School of Health Sciences, Maebashi, Japan
[c] Department of Orthopaedic Surgery, Saiseikai Maebashi Hospital, Maebashi, Japan
[d] Department of Orthopaedic Surgery, Fujioka General Hospital, Fujioka, Japan
[e] Department of Orthopaedic Surgery, Tone Central Hospital, Numata, Japan
Correspondence: Tsuyoshi Tajika, MD, PhD, Department of Rehabilitation, Graduate School of Health Sciences, Gunma University, 3-39-22 Showa-machi, Maebashi, Gunma 371-8514, Japan, E-mail: tajika@gunma-u.ac.jp

those obtained for Caucasian patients.[4] CCH injection has also been used as a minimally invasive, nonsurgical treatment option for Dupuytren's disease in Japan. Earlier studies have examined the therapeutic effects of CCH injection, the associated adverse reactions, and the recurrence rate after CCH injection.[4–10] Previous studies have also investigated the relation between upper extremity health status and psychological factors in patients with specific upper extremity disorders.[11,12] It was found that patient-reported outcome measurements for the upper extremities correlated with symptoms of depression and pain anxiety.[11] Few studies have investigated the relation between the status of the affected hand and the psychological status in patients with Dupuytren's disease. Some studies have evaluated whether the psychological status improved after treatment interventions in patients with orthopedic disease.[13,14] Nevertheless, few reports have described investigations of the association of the efficacy of CCH injection and psychological changes before and after CCH injection in patients with Dupuytren's disease. This study was conducted to evaluate the relation between the clinical outcomes of the affected hand and the depressive status and the health-related QOL before and at 6 months after CCH injection in patients with Dupuytren's disease.

METHODS

This multicenter study of 14 fingers in 14 patients (2 women and 12 men) with a mean age of 69.5 years (range 64–83 years) was conducted at four facilities. Patients evaluated consecutively between January 2019 and March 2020 were recruited.

The study inclusion criteria were as follows: diagnosis with Dupuytren's disease, testing positive in a table top test (i.e., demonstrating that the patient could not simultaneously place the affected fingers and palm flat on a table), and flexion contracture of the metacarpophalangeal (MCP) joint of between 20° and 100° or of the proximal interphalangeal (PIP) joint of between 20° and 80° in at least one digit (not the thumb).[15] We explained the advantages and disadvantages of collagenase *Clostridium histolyticum* injection therapy and fasciectomy before starting treatment. The patients who opted for nonsurgical treatment participated in this study.

Each subject completed a self-administered questionnaire with items related to sex, dominant hand, onset year of Dupuytren's disease, smoking and drinking habits/history, history of diabetes mellitus, and history of hand trauma. Patients were excluded from this study if they had had a hemorrhagic stroke or other disease affecting the hands such as rheumatoid arthritis, hand fractures, or surgery for arthritis of the finger. All procedures were carried out in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. This study was approved by Gunma University Hospital Clinical Research Review Board (Protocol Number: 2018–208). Written informed consent was obtained from all participants.

Clinical Assessment

The range of motion (ROM) of the affected fingers was measured passively in accordance with the measurement manual by hand surgeons using a stainless-steel finger goniometer before the initiation of CCH injection and at 6 months after injection.

Intervention

Collagenase *Clostridium histolyticum* (0.58 mg) was injected directly into Dupuytren's-affected cords by the hand surgeons, as described previously by Hurst et al.[15] The volumes of solution per injection were 0.25 ml for MCP joints and 0.20 ml for PIP joints.

Hand surgeons performed a standardized finger extension procedure on the affected finger 24 h after CCH injection. We instructed patients to wear night splints and to perform finger rehabilitation exercises for up to 4 months after finger extension. Patients were instructed to perform the following exercises at home four times a day for short sessions, completing ten repetitions for each exercise: (1) stretch out the fingers actively and fully, (2) make adduction and abduction movements of fingers actively and fully, (3) make full flexion of the distal interphalangeal (DIP) joint and the PIP joint with the wrist held in extension, (4) stretch out the fingers with the unaffected hand passively.

Grip Strength Measurements

A digital dynamometer (Takei Scientific Instruments, Tokyo, Japan) was used to measure the grip strength before the initiation of CCH injection and at 6 months after the injection. Grip testing was conducted using the standard position recommended by the American Society of Hand Therapists. Participants were seated with the shoulder in adduction and neutral rotation, the elbow flexed at 90°, the forearm in a neutral position, and the wrist at between 0° and 30° of extension and 0° and 15° of ulnar deviation.

Evaluation of Depression

Depression symptoms were measured using the 15-item Short Geriatric Depression Scale (GDS) both before CCH injection and at 6 months posttreatment. The diagnostic accuracy of the short form of GDS and the original version demonstrated that the accuracy of both versions of GDS was similar to that of the Center for Epidemiologic Studies Depression Scale for diagnosing depression.[16] We assessed psychological function with the 15-item Short Geriatric Depression Scale − Japanese version (GDS-J), for which overall scores of 0–5 indicate no depression, 6–8 mild depression, 9–11 moderate depression, and 12–15 severe depression.[16–19] Yaotomi evaluated the validity and reliability of GDS-J in an elderly Japanese population.[20] According to this scale, a score of 6 or higher indicates a likely depressive status.[21] All items in GDS are rated by self-report as 0 or 1, where 0 represents yes and 1 represents no. Item scores are summed, yielding a possible total score in the range 0–15. Higher scores signify a more severe depressive condition. Participants with more than one missing item were excluded from analysis.

Assessment of Hand Symptoms and Capabilities

Hand 10 is used to assess satisfaction with upper extremity function. It is a self-administered comprehensive measure that comprises ten items to identify upper extremity symptoms and the ability to perform certain activities. The ten questions were presented along with illustrations to facilitate comprehension. Each question is rated on a 0–10 numeric rating scale. The points are summed to produce a total score (minimum 0, maximum 100). A higher total score indicates a worse upper extremity function. Kurimoto et al. verified the reliability and validity of Hand 10.[22,23]

Evaluation of Health-related QOL

To evaluate the health-related QOL, we used a non-disease-specific instrument developed by the EuroQol Group: the EQ-5D-3L Japanese version.[24] The EQ-5D-3L evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension of EQ-5D-3L is assigned a response of one of three levels: no problem, some or moderate problems, or extreme problems. The EQ Visual Analog Scale (VAS) was used to measure the self-related health status of the respondents to rate their overall health. The best health status is indicated by a score of 100, whereas the worst health status carries a score of 0. Tsuchiya et al. validated EQ-5D-3L (Japanese version) as having an evaluation capacity equivalent to the original version.[25]

Statistical Analysis

Paired *t* tests or Wilcoxon signed-rank tests were used to compare changes in several variables (ROM of MCP joints, PIP joints, and DIP joints; grip strength on the affected side; the GDS-J score; the Hand 10 score; the EuroQol index score; and the EuroQol VAS score) before injection therapy and at 6 months posttreatment. Spearman's correlation coefficient by rank test was used to assess correlations between the disease duration; the change of ROM of each joint; the change of grip strength of the affected side; and the changes of the GDS-J score, the Hand 10 score, the EuroQol index score, and the EuroQol VAS score (before treatment and 6 months posttreatment). Correlations were characterized as low (r=0.10–0.29), medium (r=0.30–0.49), or high (r=0.50–1.00).[26] Data are presented as means and standard deviations. Results for which a P value of less than 0.05 was obtained were inferred to be statistically significant.

RESULTS

We treated 14 affected fingers in 14 patients with CCH injections. The follow-up period was 6 months after the CCH injection. The clinical features of patients are presented in **Table 1**. The ring finger ray was affected with a frequency of 57%, and the little finger ray was affected a frequency of 43%. Assessment using the GDS-J score revealed that, before the initiation of CCH injection therapy, 2 patients (14.3%) had mild depressive status, whereas the 12 other patients (85.7%) had no depressive status.

Significant correlations were found between the clinical findings and the evaluation items before treatment with CCH (**Table 2**). The MCP joint flexion angle (r= –0.54, P<0.05), the EuroQol index score (r= –0.57, P<0.05), and the EuroQol VAS score (r= –0.84. P<0.01) showed significant negative correlations with the GDS-J score. In contrast, the Hand 10 score (r=0.66, P<0.05) showed a significant positive correlation with the GDS-J score. The clinical outcomes obtained before CCH injection and at 6 months posttreatment are presented in **Table 3**. Adverse reactions occurred in three patients who received CCH injections: injection site laceration occurred in two patients, and injection site hematoma occurred in one patient. The severity of all adverse reactions was mild. At 6 months after CCH injection, no patient showed a depressive status, as assessed by the GDS-J score. A significant improvement was found in the extension motions of the MCP joints and PIP joints at 6 months after CCH injection

Table 1. Clinical features of the 14 participants

Characteristic	Value
Mean age (standard deviation) (years)	69.5 (5.4)
Male, n (%)	12 (86)
Family history of Dupuytren's disease, n (%)	2 (14)
Drinking history, n (%)	9 (64)
Smoking history, n (%)	8 (57)
Duration of condition (months)	53
Affected hand	
Dominant side, n (%)	7 (50)
Affected finger	
Ring finger, n (%)	8 (57)
Little finger, n (%)	6 (43)

Table 2. Correlation of clinical variables before CCH injection

	Hand 10 score	GDS-J score	EuroQol index score	EuroQol VAS score
Disease duration	–0.33	–0.39	–0.07	0.29
MCP joint extension	0.18	0.22	0.12	–0.24
MCP joint flexion	–0.57 *	–0.54 *	0.27	0.25
PIP joint extension	–0.57 *	–0.15	0.21	–0.05
PIP joint flexion	–0.16	0.25	–0.08	–0.18
DIP joint extension	–0.58 *	–0.44	0.17	0.41
DIP joint flexion	–0.02	0.12	–0.33	–0.29
Affected grip strength	–0.4	–0.34	0.06	0.01
Hand 10 score	—	0.66 *	–0.5	–0.4
GDS-J score	0.66 *	—	–0.57 *	–0.84 **
EuroQol index score	–0.5	–0.57 *	—	0.59 *
EuroQol VAS score	–0.4	–0.84 **	0.59 *	—

* Significant, P<0.05.
** Significant, P<0.01.

(MCP joint extension angle: before, −31.8°; 6 months later, −5.9°; P=0.0012. PIP joint: before, −29.1°; 6 months later, −13.8°; P=0.0095). Significant differences were found between the pre- and posttreatment EuroQol index scores and EuroQol VAS scores (EuroQol index score: before, 0.81; 6 months later, 0.97; P=0.01. EuroQol VAS score: before, 67.7; 6 months later, 88.1; P= 0.006). No significant difference was found between the grip strength of the affected hand, the Hand 10 score, and the GDS-J score before the initiation of CCH injection and at 6 months posttreatment (**Table 3**). We assessed the correlations between the differences in each clinical variable before and after CCH injection. A significant positive correlation was found between the change in the GDS-J score and the change in Hand 10 score before and after CCH injection (r=0.70, P<0.01). In contrast, significant negative correlations were found between the changes in GDS-J score and the changes in the EuroQol index score (r= –0.66, P<0.05) and the EuroQol VAS score (r= –0.66, P<0.05) before and at 6 months after CCH injection (**Table 4**).

DISCUSSION

One distinguishing characteristic of the current study is the fact that CCH therapy directly improved the health-related QOL of patients with Dupuytren's disease. The EuroQol index score and EuroQol VAS score before CCH injection treatment and at 6 months posttreatment indicated significant improvement. The Hand 10 score tended to improve after CCH injection, but the tendency was not significant.

Table 3. Clinical features before CCH injection and at 6 months posttreatment

	Before CCH injection	6 months after CCH injection	P value
MCP joint ROM (degree)			
Extension	–31.8 (24.5)	–5.9 (12.8)	0.0012 **
Flexion	82.5 (7.6)	81.8 (11.1)	0.75
PIP joint ROM (degree)			
Extension	–29.1 (27.8)	–13.8 (13.6)	0.0095 **
Flexion	94.3 (5.3)	95.5 (4.0)	0.39
DIP joint ROM (degree)			
Extension	–3.0 (5.4)	–0.7 (2.7)	0.16
Flexion	58.9 (11.2)	58.7 (16.0)	0.77
Grip strength of affected side (kg)	27.4 (8.0)	29.1 (7.4)	0.12
Hand 10 score	15.5 (16.1)	5.3 (8.0)	0.08
GDS-J score	2.2 (2.6)	1.6 (1.7)	0.40
EuroQol index score	0.81 (0.21)	0.97 (0.09)	0.011 *
EuroQol VAS score	67.7 (24.6)	88.1 (14.5)	0.006 **

Values are presented as the mean (standard deviation).
* Significant, P<0.05.
** Significant, P<0.01.

Table 4. Correlation of changes in clinical variables before CCH injection and at 6 months posttreatment

	ΔHand 10 score	ΔGDS-J score	ΔEuroQol index score	ΔEuroQol VAS score
ΔMCP joint extension	–0.38	–0.14	0.49	–0.21
ΔMCP joint flexion	–0.26	–0.08	–0.11	–0.005
ΔPIP joint extension	–0.37	–0.31	0.52	0.24
ΔPIP joint flexion	–0.15	0.04	–0.12	–0.21
ΔDIP joint extension	–0.43	–0.55 *	0.20	0.16
ΔDIP joint flexion	0.44	0.21	–0.02	–0.19
ΔAffected grip strength	–0.18	0.33	–0.24	–0.64
ΔHand 10 score	—	0.70 **	–0.35	–0.26
ΔGDS-J score	0.70 **	—	–0.66 *	–0.66 *
ΔEuroQol index score	–0.35	–0.66 *	—	0.65 *
ΔEuroQol VAS score	–0.26	–0.66 *	0.65 *	—

* Significant, P<0.05.
** Significant, P<0.01.

Earlier studies have evaluated the outcomes and efficacy of CCH treatment.[4–10]

Bradley et al. assessed patient satisfaction after CCH injection and patient-reported outcomes measured by Quick-DASH and the Southampton Dupuytren Scoring Scheme in 213 patients with Dupuytren's disease.[6] For that study, higher satisfaction was observed in patients with better improvement in hand function, and lower satisfaction was found in those with less improvement. In the current study, there was no significant association between the change before and after CCH injection in the Hand 10 score and the changes in the EuroQol index score or the EuroQol VAS score. However, there were significant associations between the change before and after CCH injections in the GDS-J score and the changes in the EuroQol index score and the EuroQol VAS score. An earlier study indicated that, from the perspective of patients with Dupuytren's disease, the performance of daily activities, interactions with others, and QOL might be more important outcomes than the degree of impairment.[27] It might be meaningful to assess the efficacy

of CCH injection using a multidisciplinary approach in patients with Dupuytren's disease.

Our study found significant improvements in the extension motion in MCP joints and in PIP joints at 6 months after CCH injection. However, no significant correlation was found between the degree of improvement of the extension ROM deficit and the Hand 10 score, the GDS-J score, the EuroQol index, or the EuroQol VAS. A previous study found correlations between objectives such as the total passive extension deficit, ROM, and subjective endpoints, with patient- and physician-rated satisfaction with therapy being low to moderate. These results suggest that objective measurements of angular deformity do not properly reflect the beneficial or otherwise effects of treatment of Dupuytren's disease.[5] Another study indicated that emotional factors and health-related QOL, not the degree of improvement of finger flexion contracture, are important contributors to functional recovery.[28] We assessed the depressive status as an emotional factor before and after CCH injection therapy. The assessment categorized by the GDS-J score revealed that 2 patients (14.3%) had mild depressive status and that 12 patients (85.7%) had no depressive status before the initiation of CCH injection therapy. However, a significant correlation was found between the GDS-J score and the Hand 10 score (r= 0.66, P< 0.05) before CCH injection. This result suggests that functional hand health status might be related to the psychological status in patients with Dupuytren's disease, as described in earlier reports.[11,12] In the current study, there was no significant difference between the GDS-J score before CCH injection and that at 6 months posttreatment. However, no patient had a depressive status 6 months after CCH injection. Furthermore, a significant positive correlation was found between the change in the GDS-J score and the change in the Hand 10 score before and at 6 months after CCH injection (r= 0.70, P<0.01). Previous studies have demonstrated that clinically positive effects of treatment intervention can improve the psychological status of patients with rheumatoid arthritis and Parkinson's Disease.[13,29] The positive clinical effects of CCH injection therapy might be associated with improvement of the depressive status and hand function in patients with Dupuytren's disease.

In our study, the incidence of adverse events such as injection site hemorrhage and skin tears was 21.4%. The severity of all adverse reactions was mild. All patients had fully healed at short-term follow-up. Earlier studies have revealed adverse events reported after treatment with CCH injection as local injection site and upper-extremity pain, peripheral edema, ecchymosis, hemorrhagic blisters, injection site hemorrhage or hematoma, skin tears, axillary or complex regional pain syndrome, tendonitis, skin graft loss, phalanx fracture, cold intolerance, digital neuropraxia, pulley rupture, and in rare cases, flexor tendon rupture.[4,30–32] Bradley et al. reported that 73% of 213 patients treated with CCH for Dupuytren contractures were very satisfied or satisfied with the CCH injection therapy outcome despite the occurrence of some adverse events such as bruising, skin split, and armpit pain.[6] Baumeister et al. reported that, as a general principle, an adverse occurrence has a greater effect on overall satisfaction than an advantageous one across a broad range of psychological phenomena.[33] It is evidently very important for the physician to carefully give sufficient information related to possible adverse effects and to inform patients about complications and recurrence rates before obtaining consent for CCH injection therapy.

This study has several noteworthy limitations. First, the small sample size influenced the statistical power for assessing relationships between the changes recorded in the clinical findings. Further work is needed to re-evaluate the current conclusions using a more appropriate sample size. Second, we were unable to investigate the clinical outcomes of CCH injection in the long term. Earlier studies demonstrated that CCH injection therapy is associated with a low rate of severe complications but a high recurrence rate.[34] In our study, no recurrence was found in any patient. Recurrence of this disease could influence the psychological status of patients. Third, the use of different self-administered questionnaires to assess depression might engender overestimation or underestimation of depressive symptom responses. Additional psychosocial assessment tools might affect the results related to depression status. Fourth, we did not assess other related factors for depressive symptoms such as Japanese cultural factors, education level/socioeconomic status, or other unrelated health concerns. Fifth, the responsiveness of EQ-5D-3L and Hand 10 has not been evaluated specifically for patients with Dupuytren's disease. Trybus et al. described the Dupuytren Disease Scale of Subjective Wellbeing of Patients, a 12-item questionnaire covering four subscales consisting of self-esteem, family life, occupational life, and social life, to evaluate the QOL of the patients with Dupuytren's disease.[35] Responsiveness indicates an instrument's ability to capture clinically important changes[36]; valid reproducible, responsive Dupuytren's disease-specific measures should be developed.

CONCLUSIONS

Our results demonstrated that, in patients with Dupuytren's disease before CCH injection, the level of functionality of the affected hand and the health-related QOL were associated with the depressive status level. CCH injection therapy directly improved health-related QOL, but not depression status, in patients with Dupuytren's disease at 6 months posttreatment. However, the change in the GDS-J score from before CCH injection to 6 months posttreatment showed significant correlations with the changes in the Hand 10 score, the EuroQol index score, and the EuroQol VAS score. Positive change in depressive status could be associated with improvements of the affected hand function and health-related QOL.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

REFERENCES

1. Bayat A, McGrouther DA: Management of Dupuytren's disease – clear advice for an elusive condition. Ann R Coll Surg Engl 2006;88:3–8. DOI:10.1308/003588406X83104, PMID:16460628
2. Engstrand C, Borén L, Liedberg GM: Evaluation of activity limitation and digital extension in Dupuytren's contracture three months after fasciectomy and hand therapy interventions. J Hand Ther 2009;22:21–27, quiz 27. DOI:10.1016/j.jht.2008.08.003, PMID:18986794
3. Tajika T, Kobayashi T, Kaneko T, Tsunoda D, Tsunoda K, Sutou T, Yamamoto A, Takagishi K: Epidemiological study for personal risk factors and quality of life related to Dupuytren's disease in a mountain village of Japan. J Orthop Sci 2014;19:64–70. DOI:10.1007/s00776-013-0478-y, PMID:24129389
4. Hirata H, Tanaka K, Sakai A, Kakinoki R, Ikegami H, Tateishi N: Efficacy and safety of collagenase *Clostridium histolyticum* injection for Dupuytren's contracture in non-Caucasian Japanese patients (CORD-J Study): the first clinical trial in a non-Caucasian population. J Hand Surg Eur Vol 2017;42:30–38. DOI:10.1177/1753193416653249, PMID:27313184
5. Warwick D, Arner M, Pajardi G, Reichert B, Szabo Z, Masmejean EH, Fores J, Chapman DS, Gerber RA, Huard F, Seghouani A, Szczypa PP, POINT X Investigators: Collagenase *Clostridium histolyticum* in patients with Dupuytren's contracture: results from POINT X, an open-label study of clinical and patient-reported outcomes. J Hand Surg Eur Vol 2015;40:124–132. DOI:10.1177/1753193413519926, PMID:24470559
6. Bradley J, Warwick D: Patient satisfaction with collagenase. J Hand Surg Am 2016;41:689–697. DOI:10.1016/j.jhsa.2016.03.003, PMID:27132016
7. Nordenskjöld J, Lauritzson A, Åkesson A, Atroshi I: Collagenase injections for Dupuytren disease: 3-year treatment outcomes and predictors of recurrence in 89 hands. Acta Orthop 2019;90:517–522. DOI:10.1080/17453674.2019.1663472, PMID:31500473
8. Zhang D, Earp BE, Benavent KA, Blazar P: Collagenase treatment of Dupuytren's disease with minimum 5-year follow-up: recurrence, reintervention, and satisfaction. Plast Reconstr Surg 2020;146:1071–1079. DOI:10.1097/PRS.0000000000007243, PMID:33136952
9. Cooper TB, Poonit K, Yao C, Jin Z, Zheng J, Yan H: The efficacies and limitations of fasciectomy and collagenase *Clostridium histolyticum* in Dupuytren's contracture management: a meta-analysis. J Orthop Surg (Hong Kong) 2020;28: 2309499020921747. DOI:10.1177/2309499020921747, PMID:32484064
10. David M, Smith G, Pinder R, Craigen M, Waldram M, Mishra A, Dickson D, Wu F, Brewster M: Outcomes and early recurrence following enzymatic (collagenase) treatment of moderate and severe Dupuytren contractures. J Hand Surg Am 2020;45:1187.e1–1187.e11. DOI:10.1016/j.jhsa.2020.06.012, PMID:32861504
11. Ring D, Kadzielski J, Fabian L, Zurakowski D, Malhotra LR, Jupiter JB: Self-reported upper extremity health status correlates with depression. J Bone Joint Surg Am 2006;88:1983–1988. PMID:16951115
12. Das De S, Vranceanu AM, Ring DC: Contribution of kinesophobia and catastrophic thinking to upper-extremity-specific disability. J Bone Joint Surg Am 2013;95:76–81.
13. Miwa Y, Hosaka M, Ohtsuka K, Sato M, Takahashi R, Wakabayashi K, Odai T, Yajima N, Kasama T: Depression is improved when low-dose tacrolimus is given to rheumatoid arthritis patients showing an inadequate response to biologic agents. Mod Rheumatol 2013;23:920–924. DOI:10.3109/s10165-012-0765-z, PMID:22990336

14. Park C, Garcia AN, Cook C, Gottfried ON: Effect of change in preoperative depression/anxiety on patient outcomes following lumbar spine surgery. Clin Neurol Neurosurg 2020;199:106312. DOI:10.1016/j.clineuro.2020.106312, PMID:33069091
15. Hurst LC: Dupuytren's Contracture. Green's operative hand surgery. 6th Edn. (eds Wolfe SW). Philadelphia, Churchill Livingstone, 2010; 141–158.
16. Lesher EL, Berryhill JS: Validation of the Geriatric Depression Scale–Short Form among inpatients. J Clin Psychol 1994;50:256–260.
17. Wancata J, Alexandrowicz R, Marquart B, Weiss M, Friedrich F: The criterion validity of the Geriatric Depression Scale: a systematic review. Acta Psychiatr Scand 2006;114:398–410. DOI:10.1111/j.1600-0447.2006.00888.x, PMID:17087788
18. Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO: Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982-1983–1983;17:37–49. DOI:10.1016/0022-3956(82)90033-4, PMID:7183759
19. Burke WJ, Roccaforte WH, Wengel SP: The short form of the Geriatric Depression Scale: a comparison with the 30-item form. J Geriatr Psychiatry Neurol 1991;4:173–178. PMID:1953971
20. Yaotomi N: The factor structure and item characteristics of the GDS (Geriatric Depression Scale) short version in a Japanese elderly sample [in Japanese]. Ronen Shakai Kagaku. 1994;16:29–36.
21. Yesavage JA, Sheikh JI: 9/Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. Clin Gerontol 1986;5:165–173. DOI:10.1300/J018v05n01_09
22. Kurimoto S, Yamamoto M, Shinohara T, Tatebe M, Katsuyuki I, Hirata H: Favorable effects of explanatory illustrations attached to a self-administered questionnaire for upper extremity disorders. Qual Life Res 2013;22:1145–1149. DOI:10.1007/s11136-012-0233-4, PMID:22820834
23. Kurimoto S, Suzuki M, Yamamoto M, Okui N, Hirata H, Imaeda T: Development and validation of a ten-item questionnaire with explanatory illustrations to assess upper extremity disorders: favorable effect of illustrations in the item reduction process. J Orthop Sci 2011;16:737–744. DOI:10.1007/s00776-011-0148-x, PMID:21912917
24. EuroQol Group: EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208. DOI:10.1016/0168-8510(90)90421-9, PMID:10109801
25. Tsuchiya A, Ikeda S, Ikegami N, Nishimura S, Sakai I, Fukuda T, Hamashima C, Hisashige A, Tamura M: Estimating an EQ-5D population value set: the case of Japan. Health Econ 2002;11:341–353. DOI:10.1002/hec.673, PMID:12007165
26. Cohen J, Cohen P, Weat SG, Aiken LS: Applied multiple regression/correlation analysis for the behavioral science, Third edn. Hillsdale, NJ: Lawrence Erlbaum Associates, 2003
27. Wilburn J, McKenna SP, Perry-Hinsley D, Bayat A: The impact of Dupuytren disease on patient activity and quality of life. J Hand Surg Am 2013;38:1209–1214. DOI:10.1016/j.jhsa.2013.03.036, PMID:23707018
28. Engstrand C, Krevers B, Kvist J: Factors affecting functional recovery after surgery and hand therapy in patients with Dupuytren's disease. J Hand Ther 2015;28:255–260, quiz 260. DOI:10.1016/j.jht.2014.11.006, PMID:25998546
29. Nielsen C, Siersma V, Ghaziani E, Beyer N, Magnusson SP, Couppé C: Health-related quality of life and physical function in individuals with Parkinson's disease after a multidisciplinary rehabilitation regimen—a prospective cohort feasibility study. Int J Environ Res Public Health 2020;17:7668. DOI:10.3390/ijerph17207668, PMID:33096677
30. Swanson JW, Watt AJ, Vedder NB: Skin graft loss resulting from collagenase *Clostridium histolyticum* treatment of Dupuytren contracture: case report and review of the literature. J Hand Surg Am 2013;38:548–551.
31. Cheung K, Walley KC, Rozental TD: Management of complications of Dupuytren contracture. Hand Clin 2015;31:345–354.
32. Lewallen LW, Rizzo M: Phalangeal fracture during attempted Dupuytren's release following *Clostridium collagenase* injection: case report. J Orthop Case Rep 2017;7:21–24.
33. Baumeister RF, Bratslavsky E, Finkenauer C, Vohs KD: Bad is stronger than good. Rev Gen Psychol 2001;5:323–370. DOI:10.1037/1089-2680.5.4.323

34. Peimer CA, Blazar P, Coleman S, Kaplan FT, Smith T, Lindau T: Dupuytren contracture recurrence following treatment with collagenase *Clostridium histolyticum* (CORDLESS [Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study]): 5-year data. J Hand Surg Am 2015;40:1597–1605. DOI:10.1016/j.jhsa.2015.04.036, PMID:26096221
35. Trybus M, Bednarek M, Lorkowski J, Teul I: Psychologic aspects of Dupuytren's disease: a new scale of subjective well-being of patients. Ann Acad Med Stetin 2011;57:31–37, discussion 37. PMID:22593988
36. Deyo RA, Diehr P, Patrick DL: Reproducibility and responsiveness of health status measures statistics and strategies for evaluation. Control Clin Trials 1991;12(Suppl):S142–S158. DOI:10.1016/S0197-2456(05)80019-4, PMID:1663851