

Nagoya J. Med. Sci. **85**. 659–667, 2023
doi:10.18999/nagjms.85.4.659

Hand function and quality of life in patients with diabetes mellitus before and during the COVID-19 pandemic

Michiro Yamamoto¹, Yayoi Kato² and Jun Takeuchi²

¹*Department of Human Enhancement and Hand Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan*
²*Sapporo Diabetes and Thyroid Clinic, Sapporo, Japan*

ABSTRACT

This study aimed to investigate the effects of the coronavirus disease 2019 (COVID-19) pandemic on patients with diabetes mellitus using patient-rated outcome measures focusing on hand function and quality of life, as well as patients' mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It was a part of a longitudinal research involving patients with diabetes mellitus living in Sapporo, Japan. Among the 594 patients surveyed before the COVID-19 pandemic from March to June 2019, 417 patients who could be re-surveyed from March to June 2021 were included. We compared the patient-rated outcome measures, namely the Hand10 for hand function and EuroQol five-dimension questionnaire for assessing quality of life in the same population of patients with diabetes mellitus, before and during the COVID-19 pandemic. The results indicated no deterioration in the Hand10 (3.9 vs 3.6) and quality of life scores (0.89 vs 0.9), including mobility (1.25 vs 1.17), self-care (1.1 vs 1.08), pain/discomfort (1.43 vs 1.35), and anxiety/depression (1.21 vs 1.2), during the COVID-19 pandemic when compared with the pre-pandemic values. Usual activity values on the EuroQol five-dimension subscale significantly improved during the pandemic compared to those before the pandemic (1.21 vs 1.12, $p < 0.01$). This study highlighted the effects of the COVID-19 pandemic on patients with diabetes mellitus by comparing patient-rated outcome measures in two different social situations. Patients with diabetes mellitus living in Sapporo, Japan maintained hand function and quality of life by continuing their usual activities during the COVID-19 pandemic.

Keywords: hand function, quality of life, diabetes mellitus, COVID-19 pandemic

Abbreviations:

COVID-19: coronavirus disease 2019

DM: diabetes mellitus

QOL: quality of life

EQ-5D: EuroQol five-dimension

BMI: body mass index

HbA1c: glycosylated hemoglobin

This is an Open Access article distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Received: June 1, 2023; accepted: June 13, 2023

Corresponding Author: Michiro Yamamoto, MD, PhD

Department of Human Enhancement and Hand Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan

TEL: +81-52-744-2957, Fax: +81-52-744-2964, E-mail: michi-ya@med.nagoya-u.ac.jp

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has been shown to affect individuals by increasing the incidence of depression, anxiety, and stress, as well as exacerbating physical symptoms, such as insomnia and musculoskeletal pain.¹⁻³ On contrary, some reports have indicated little differences in the scores of patient-rated outcome measures regarding the quality of life (QOL) and physical function before and during the pandemic.^{4,5}

Patients with diabetes mellitus (DM) are known to be at an increased risk of infection. A report published by the Chinese Center for Disease Control and Prevention involving 72,314 cases of COVID-19 revealed increased mortality among patients with DM (overall, 2.3%; diabetic patients, 7.3%).⁶ Therefore, patients with DM may have experienced greater psychological and physical impact during the COVID-19 pandemic compared to those of the general population.

DM has been identified as an etiologic factor for several conditions affecting the hand, including limited joint mobility, Dupuytren's contracture, carpal tunnel syndrome, and trigger finger.^{7,8} The spectrum of hand disorders associated with DM is referred to as the "diabetic hand."

In March 2019, we conducted a longitudinal study on hand function and QOL in patients visiting a specialized DM outpatient clinic. We used the patient-rated outcome measures, namely the Hand10 and EuroQol five-dimension (EQ-5D) questionnaires to evaluate hand function and QOL, respectively.^{9,10} We compared the outcomes and patient background data before and during the COVID-19 pandemic.

This study aimed to investigate the effects of the COVID-19 pandemic in patients with DM by comparing patient-rated outcome measures related to hand function and QOL, as well as patients' mobility, self-care, usual activities, pain/discomfort, and anxiety/depression using the EQ-5D subscales.

MATERIALS AND METHODS

We conducted a longitudinal study on hand function and QOL among patients with DM in collaboration with a physician specializing in DM and a hand surgery specialist. This study was approved by the institutional review boards of the authors' affiliated institutions. Informed consent was obtained from all patients. The study adhered to the principles of the Declaration of Helsinki.

Among the 594 patients surveyed before the COVID-19 pandemic from March to June 2019, 417 patients who could be re-surveyed from March to June 2021 were included. Consecutive outpatients, aged >18 years, with DM were included. The exclusion criteria were patients who could not speak Japanese or those who had a history of rheumatoid arthritis or hand disorders other than those associated with DM. These exclusion criteria were selected because we wanted to assess patients with diabetic hand, excluding those with rheumatoid hand or hand osteoarthritis.

Clinical diagnosis of diabetic hand

The hands and wrists of the patients were examined by a physician under the supervision of a hand surgery specialist.

Limited joint mobility was evaluated with or without the "prayer sign."^{11,12} Patients were asked to emulate praying and if the metacarpophalangeal or proximal interphalangeal joints of both the hands were not touching, the prayer sign was assessed as positive.

Dupuytren's contracture was diagnosed if palmar or digital nodules and cords, skin tethering, or digital contracture were present.¹³

Patients with pain, numbness, and paresthesia from the thumb to the radial side of the ring

finger and positive findings in provocative tests, such as Tinel's sign and Phalen's test, were diagnosed with carpal tunnel syndrome. Electrophysiological assessments of the median nerve were conducted in patients with positive physical findings. A diagnosis of carpal tunnel syndrome was confirmed if the sensory nerve conduction velocity was <49 m/s and distal motor latency was >4.5 ms.^{7,14}

Trigger finger was diagnosed by observation of palpable crepitus at the A1 pulley, locking of a digit in flexion or extension, or both.¹⁵

Patients were diagnosed with a diabetic hand if they exhibited at least one of these hand abnormalities.

Three major complications of diabetes and foot lesions

Ophthalmologists assessed retinopathy based on the Davis classification and graded it as no diabetic retinopathy, simple diabetic retinopathy, or proliferative diabetic retinopathy.¹⁶ Both simple and proliferative diabetic retinopathy were categorized as retinopathy.

For the diagnosis of diabetic neuropathy, patients were interviewed about neurological symptoms and comprehensively examined for sensations, such as pain (using a toothpick/bamboo skewer), vibration (using a C128 tuning fork), and pressure (using a monofilament). The Achilles' tendon reflex was also evaluated as a part of the assessment.¹⁷

Diabetic nephropathy was diagnosed at any stage as follows: microalbuminuria (albumin excretion of 30–300 mg/day) or macroalbuminuria (albumin excretion of >300 mg/day).¹⁸

Diabetic foot was defined as infections, ulcers, and destructive lesions occurring in the lower limb tissues of patients with DM, which were associated with an ongoing neuropathy and peripheral artery disease.¹⁷

Patient-rated outcome measures

The Hand10 questionnaire was used to evaluate hand function.⁹ The Hand10 is a shortened version of the Hand20 questionnaire.¹⁹ It consists of ten self-reported questions designed to assess upper extremity symptoms and disability. The Hand10 scores range from 0 to 100, with higher scores indicating lower hand function. The Hand10 had illustrations accompanying each question, which promoted comprehension of the text and motivated the patients to answer the items correctly.²⁰

The patients also completed the 5-level EQ-5D (EQ-5D-5L), comprising of the following five domains: (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression.¹⁰ It is the most commonly used QOL instrument worldwide and includes a “crosswalk” to convert the QOL into utility values. The QOL scores range from 0 to 1, with higher scores indicating better QOL. The EQ-5D-5L is available in Japanese and has been validated for use in participants aged ≥ 12 years.²¹

Evaluations

Initially, we compared basic patient data, including age, sex, type of diabetes, duration of diabetes, body mass index (BMI), glycosylated hemoglobin (HbA1c) level, Hand10 score, and EQ-5D score, based on the presence or absence of the three major complications or diabetic hand using the pre-COVID-19 data.

Subsequently, we compared the basic patient data, morbidity related to the diabetic hand, Hand10 score, EQ-5D score, and EQ-5D subscale scores before and during the COVID-19 pandemic.

Statistical analysis

Data were analyzed using the t-test or chi-square test. Statistical significance was set at $p < 0.05$.

RESULTS

Patient demographics

Altogether, 417 patients with DM (mean age: 57 years, males: 253 [61%], type 2 diabetes: 391 [94%], mean BMI: 26 kg/m², mean duration of diabetes: 9.1 years) were included in this study. Among them, 164 (37%) patients exhibited at least one of three major complications or foot lesions, and 121 (29%) patients exhibited at least one criterion for diabetic hand (Table 1).

Table 1 Characteristics of participants

Number of participants	417
Age, years (mean \pm SD)	57 \pm 13
Sex: male, n (%)	253 (61%)
Type 2 diabetes, n (%)	391 (94%)
BMI, kg/m ² (mean \pm SD)	26 \pm 4.9
Duration of diabetes, years (mean \pm SD)	9.1 \pm 7.9
Retinopathy, n (%)	66 (16%)
Nephropathy, n (%)	119 (29%)
Peripheral neuropathy, n (%)	45 (11%)
Foot lesion, n (%)	3 (0.7%)
Limited joint mobility of the finger, n (%)	61 (15%)
Dupuytren's contracture, n (%)	7 (1.7%)
Trigger finger, n (%)	63 (15%)
Carpal tunnel syndrome, n (%)	25 (4.3%)

n: number

BMI: body mass index

SD: standard deviation

Presence or absence of the three major diabetic complications

Patients having the three major complications (retinopathy, neuropathy, or nephropathy) were older (59.7 years vs 56.4 years), had a longer duration of illness (11.2 years vs 7.8 years), and exhibited significantly higher BMI (26.8 kg/m² vs 25.3 kg/m²) and HbA1c level (7.49% vs 7.03%) than patient without these major complications. Although no significant difference was observed in the Hand10 score (4 vs 3.8), the QOL score was significantly lower among patients with these major complications (0.87 vs 0.9) (Table 2).

Table 2 Comparison of patients with or without three major diabetic complications

	With three major complications	Without three major complications	P-value
Number	164	253	
Age, years (mean ± SD)	59.7 ± 13.5	56.4 ± 12.7	p < 0.05
Sex: male, n (%)	98 (60%)	155 (61%)	p = 0.84
Type 2 diabetes, n (%)	157 (96%)	234 (92%)	p = 0.26
Duration of diabetes, years (mean ± SD)	11.2 ± 9	7.8 ± 6.8	p < 0.01
BMI, kg/m² (mean ± SD)	26.8 ± 4.7	25.3 ± 4.9	p < 0.01
HbA1c, % (mean ± SD)	7.49 ± 1.5	7.03 ± 1	p < 0.01
Hand10 score (mean ± SD)	4 ± 7.5	3.8 ± 10.6	p = 0.86
EQ-5D index score (mean ± SD)	0.87 ± 0.16	0.9 ± 0.14	p < 0.05

n: number

BMI: body mass index

SD: standard deviation

EQ-5D: EuroQol five-dimension

Presence or absence of diabetic hand

The group with diabetic hand was significantly older (63 years vs 55.6 years), had fewer males (50% vs 65%), and exhibited a longer duration of diabetes (11.6 years vs 8.1 years) than those of the group without diabetic hand. No significant differences were observed in BMI (26.3 kg/m² vs 25.7 kg/m²) and HbA1c level (7.27% vs 7.19%) between the groups. The Hand10 score (6.7 vs 2.7) was significantly higher and QOL score (0.83 vs 0.91) was significantly lower in the diabetic hand group (Table 3).

Table 3 Comparison of patients with or without diabetic hand

	With diabetic hand	Without diabetic hand	P-value
Number	121	296	
Age, years (mean ± SD)	63 ± 11.6	55.6 ± 13.1	p < 0.01
Sex: male, n (%)	61 (50%)	192 (65%)	p < 0.01
Type 2 diabetes, n (%)	113 (93%)	278 (94%)	p = 0.98
Duration of diabetes, years (mean ± SD)	11.6 ± 9.9	8.1 ± 6.7	p < 0.01
BMI, kg/m² (mean ± SD)	26.3 ± 5.7	25.7 ± 4.5	p = 0.18
HbA1c, % (mean ± SD)	7.27 ± 1.1	7.19 ± 1.3	p = 0.54
Hand10 score (mean ± SD)	6.7 ± 10.3	2.7 ± 8.9	p < 0.01
EQ-5D index score (mean ± SD)	0.83 ± 0.16	0.91 ± 0.14	p < 0.01

n: number

BMI: body mass index

SD: standard deviation

EQ-5D: EuroQol five-dimension

Comparison before and during the COVID-19 pandemic

Comparison between the data obtained before and during the COVID-19 pandemic revealed no significant differences in BMI (25.9 kg/m² vs 25.6 kg/m²), HbA1c level (7.21% vs 7.08%), and the proportion of patients with diabetic hands (29% vs 30%). The Hand10 (3.9 vs 3.6), QOL (0.89 vs 0.9), and EQ-5D subscale scores for mobility (1.25 vs 1.17), self-care (1.1 vs 1.08), pain/discomfort (1.43 vs 1.35), and anxiety/depression (1.21 vs 1.2) demonstrated no deterioration during the pandemic. Only the scores for the usual activities domain of the EQ-5D subscale significantly improved during the pandemic (1.21 vs 1.12, p<0.01) (Table 4).

Table 4 Comparison of 417 patients pre- and during COVID-19 pandemic

	Pre-COVID-19 pandemic	During COVID-19 pandemic	P-value
BMI, kg/m² (mean ± SD)	25.9 ± 4.9	25.6 ± 4.7	p = 0.5
HbA1c, % (mean ± SD)	7.21 ± 1.2	7.08 ± 1.1	p = 0.11
Diabetic hand, n (%)	122 (29%)	126 (30%)	p = 0.82
Hand10 score (mean ± SD)	3.9 ± 9.5	3.6 ± 9.2	p = 0.61
EQ-5D index score (mean ± SD)	0.89 ± 0.2	0.9 ± 0.1	p = 0.15
EQ-5D subscale mobility	1.25 ± 0.6	1.17 ± 0.5	p = 0.07
EQ-5D subscale self-care	1.1 ± 0.4	1.08 ± 0.3	p = 0.25
EQ-5D subscale usual activities	1.21 ± 0.5	1.12 ± 0.4	p < 0.01
EQ-5D subscale pain/discomfort	1.43 ± 0.8	1.35 ± 0.6	p = 0.1
EQ-5D subscale anxiety/depression	1.21 ± 0.5	1.2 ± 0.5	p = 0.75

BMI: body mass index

SD: standard deviation

EQ-5D: EuroQol five-dimension

DISCUSSION

In the present study, a comparison of patients with DM before and during the COVID-19 pandemic revealed no deterioration in hand function or QOL, including mobility, self-care, pain/discomfort, and anxiety/depression. Patients with DM living in Sapporo continued their usual activities and maintained their QOL during the pandemic.

This study was a part of a longitudinal research investigating hand function and QOL among patients with DM, in collaboration with a physician specializing in DM and a hand surgery specialist. Cohen et al reported that the COVID-19 pandemic and its associated lockdown had no influence on the QOL but little influence on secondary outcomes among the participants included in the Hand-wrist study cohort in the Netherlands.⁴ However, since the authors compared different patient populations with hand and wrist conditions during the pandemic and reference period, baseline differences in terms of unidentified covariates might represent a major limitation. We compared the same patient population in two different social situations. Therefore, our study demonstrated the pure effect of the COVID-19 pandemic on patients with DM.

We also investigated the impact on QOL and hand function in patients with or without the three major complications of DM and diabetic hand. Patients with these three major complications or foot lesions were significantly older and had a longer duration of illness than those in

the patients without these complications; additionally, BMI and HbA1c levels were significantly higher in these patients. Adherence to medications and lifestyle modifications, including weight loss, increased physical activity, and adoption of a healthy diet, are important for reducing the risk of complications.²²

The characteristics of diabetic hands differed according to the presence or absence of the three major complications. Significant differences were observed in age, duration of illness, and sex among these patients; however, no significant differences were observed in HbA1c level or BMI. Aging of the hands and long-term illnesses associated with DM are believed to be involved in the onset of diabetic hand. Moreover, women are at a higher risk of developing diabetic hands. Controlling blood glucose levels and BMI alone is insufficient for preventing diabetic hand, and other approaches against hand aging may be required. Several pathological mechanisms are conceivable for the development of diabetic hand. Long-standing diabetes, suboptimal glycemic control, microangiopathy, and genetic factors have been considered responsible for the development of diabetic hand.¹² Recent advances in geriatric science have revealed an accumulation of senescent cells in the tissues of patients with DM. The diabetic microenvironment is believed to promote cellular senescence in various tissues.²³ The senescence-associated secretory phenotype may result in diabetic hands due to increased levels of transforming growth factor, vascular endothelial growth factor, and interleukin-6 in the tissues of patients with Dupuytren's contracture or carpal tunnel syndrome.²⁴⁻²⁶

This study had several limitations. First, the sample cohort surveyed was relatively small and may have been numerically insufficient. Nevertheless, very few reports have compared the same patient population before and during the pandemic. Therefore, we considered these data to be valuable. Second, only the patients living in the suburbs of Sapporo City, Japan were included. The impact of COVID-19 has varied across countries. However, in May 2021, a medical emergency was declared in Sapporo due to the rapid increase in the number of patients with coronavirus infection. Sapporo is one of the Japanese cities that was severely affected by the COVID-19 pandemic. Therefore, this study highlighted the effects of the COVID-19 pandemic on patients with DM by comparing patient-rated outcome measures in two different social situations.

CONCLUSION

We compared the hand function and QOL of patients with DM before and during the COVID-19 pandemic. Although the presence of the three major diabetic complications and diabetic hand significantly impacted the QOL in patients with DM, the COVID-19 pandemic did not affect the QOL and EQ-5D subscale scores for movement, self-care, pain/discomfort, and anxiety/depression. Patients with DM living in Sapporo, Japan maintained their QOL by continuing their usual activities.

ACKNOWLEDGMENTS

We would like to express our appreciation to James Curley, BA, for his work.

AUTHORS' CONTRIBUTIONS

Study concept and design: Yamamoto and Takeuchi.

Acquisition of data: Kato and Takeuchi.

Drafting of the manuscript: Yamamoto and Takeuchi.

Statistical analysis and interpretation of the data: Yamamoto.

Study supervision: Yamamoto and Takeuchi.

All authors were involved in the writing and revision of the manuscript and have approved the manuscript for publication.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

- 1 Douglas M, Katikireddi SV, Taulbut M, McKee M, McCartney G. Mitigating the wider health effects of covid-19 pandemic response. *BMJ*. 2020;369:m1557. doi:10.1136/bmj.m1557.
- 2 Joseph SJ, Shoib S, Sg T, Bhandari SS. Psychological concerns and musculoskeletal pain amidst the COVID-19 lockdown. *Open J Psychiatry Allied Sci*. 2020;11(2):137–139. doi:10.5958/2394-2061.2020.00026.9.
- 3 Kasturi S, Price LL, Paushkin V, Salmon JE, McAlindon TE, Mandl LA. Impact of the first wave of the COVID-19 pandemic on systemic lupus erythematosus patients: Results from a multi-center prospective cohort. *Lupus*. 2021;30(11):1747–1755. doi:10.1177/09612033211033981.
- 4 Cohen A, Selles RW, De Ridder WA, et al. What Is the Impact of the COVID-19 Pandemic on Quality of Life and Other Patient-reported Outcomes? An Analysis of the Hand-Wrist Study Cohort. *Clin Orthop Relat Res*. 2021;479(2):335–345. doi:10.1097/CORR.0000000000001514.
- 5 Bargon CA, Batenburg MCT, van Stam LE, et al. Impact of the COVID-19 pandemic on patient-reported outcomes of breast cancer patients and survivors. *JNCI Cancer Spectr*. 2020;5(1):pkaa104. doi:10.1093/jncics/pkaa104.
- 6 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239–1242. doi:10.1001/jama.2020.2648.
- 7 Al-Matubsi HY, Hamdan F, Alhanbali OA, Oriquat GA, Salim M. Diabetic hand syndromes as a clinical and diagnostic tool for diabetes mellitus patients. *Diabetes Res Clin Pract*. 2011;94(2):225–229. doi:10.1016/j.diabres.2011.07.012.
- 8 Chammas M, Bousquet P, Renard E, Poirier JL, Jaffiol C, Allieu Y. Dupuytren's disease, carpal tunnel syndrome, trigger finger, and diabetes mellitus. *J Hand Surg Am*. 1995;20(1):109–114. doi:10.1016/S0363-5023(05)80068-1.
- 9 Kurimoto S, Suzuki M, Yamamoto M, Okui N, Imaeda T, Hirata H. 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(6):737–744. doi:10.1007/s00776-011-0148-x.
- 10 EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199–208. doi:10.1016/0168-8510(90)90421-9.
- 11 Abate M, Schiavone C, Salini V, Andia I. Management of limited joint mobility in diabetic patients. *Diabetes Metab Syndr Obes*. 2013;6:197–207. doi:10.2147/DMSO.S33943.
- 12 Gamstedt A, Holm-Glad J, Ohlson CG, Sundström M. Hand abnormalities are strongly associated with the duration of diabetes mellitus. *J Intern Med*. 1993;234(2):189–193. doi:10.1111/j.1365-2796.1993.tb00729.x.
- 13 Noble J, Heathcote JG, Cohen H. Diabetes mellitus in the aetiology of Dupuytren's disease. *J Bone Joint Surg Br*. 1984;66(3):322–325. doi:10.1302/0301-620X.66B3.6725338.
- 14 Shivde AJ, Dreizin I, Fisher MA. The carpal tunnel syndrome. A clinical - electrodiagnostic analysis. *Electromyogr Clin Neurophysiol*. 1981;21(2–3):143–153.
- 15 Kuczmarski AS, Harris AP, Gil JA, Weiss AC. Management of diabetic trigger finger. *J Hand Surg Am*. 2019;44(2):150–153. doi:10.1016/j.jhsa.2018.03.045.
- 16 Tanaka K, Kawai T, Saisho Y, et al. Relationship between stage of diabetic retinopathy and pulse wave velocity in Japanese patients with type 2 diabetes. *J Diabetes Res*. 2013;2013:193514. doi:10.1155/2013/193514.
- 17 Haneda M, Noda M, Origasa H, et al. Japanese clinical practice guideline for diabetes 2016. *Diabetol Int*.

- 2018;9(1):1–45. doi:10.1007/s13340-018-0345-3.
- 18 Strippoli GF, Craig M, Deeks JJ, Schena FP, Craig JC. Effects of angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists on mortality and renal outcomes in diabetic nephropathy: systematic review. *BMJ*. 2004;329(7470):828. doi:10.1136/bmj.38237.585000.7C.
 - 19 Suzuki M, Kurimoto S, Shinohara T, Tatebe M, Imaeda T, Hirata H. Development and validation of an illustrated questionnaire to evaluate disabilities of the upper limb. *J Bone Joint Surg Br*. 2010;92(7):963–969. doi:10.1302/0301-620X.92B7.23410.
 - 20 Kurimoto S, Yamamoto M, Shinohara T, Tatebe M, Iwatsuki K, Hirata H. Favorable effects of explanatory illustrations attached to a self-administered questionnaire for upper extremity disorders. *Qual Life Res*. 2013;22(5):1145–1149. doi:10.1007/s11136-012-0233-4.
 - 21 Tsuchiya A, Ikeda S, Ikegami N, et al. Estimating an EQ-5D population value set: the case of Japan. *Health Econ*. 2002;11(4):341–353. doi:10.1002/hec.673.
 - 22 Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol*. 2018;14(2):88–98. doi:10.1038/nrendo.2017.151.
 - 23 Palmer AK, Tchkonja T, LeBrasseur NK, Chini EN, Xu M, Kirkland JL. Cellular senescence in type 2 diabetes: a therapeutic opportunity. *Diabetes*. 2015;64(7):2289–2298. doi:10.2337/db14-1820.
 - 24 Freeland AE, Tucci MA, Barbieri RA, Angel MF, Nick TG. Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. *Microsurgery*. 2002;22(8):378–385. doi:10.1002/micr.10065.
 - 25 Tucci M, Barbieri R, Freeland A. Biochemical and histological analysis of the flexor tenosynovium in patients with carpal tunnel syndrome. *Biomed Sci Instrum*. 1997;33:246–251.
 - 26 Sharma D, Jaggi AS, Bali A. Clinical evidence and mechanisms of growth factors in idiopathic and diabetes-induced carpal tunnel syndrome. *Eur J Pharmacol*. 2018;837:156–163. doi:10.1016/j.ejphar.2018.08.017.