

Diabetic hand: prevalence and incidence of diabetic hand problems using data from 1.1 million inhabitants in southern Sweden

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ABSTRACT

Introduction ‘The diabetic hand’ has traditionally referred to hand complications due to diabetes mellitus (DM), including trigger finger (TF) and Dupuytren’s disease (DD). Recent publications have also proposed DM as a risk factor for carpal tunnel syndrome (CTS), ulnar nerve entrapment (UNE), and possibly osteoarthritis (OA) of the first carpometacarpal (CMC-1) joint. This study aimed to explore prevalence and incidence of diabetic hand complications among the population in southern Sweden.

Research design and methods Approximately 1.1 million inhabitants in the region of Skåne aged ≥ 18 years, whereof 50 000 with DM, were included. Data on incident CTS, UNE, TF, DD, and OA of the CMC-1 joint between 2004 and 2019 were collected from the Skåne Healthcare Register and cross-linked with the National Diabetes Register. Prevalences on December 31, 2019 and 10-year incidence ratios were calculated for type 1 diabetes (T1D), type 2 diabetes (T2D), and the population without DM, stratified for sex. Prevalence ratios and incidence rate ratios with 95% CIs were used for group comparisons.

Results The prevalences of all five studied diagnoses were higher in both men and women with T1D and T2D ($p < 0.01$) and both T1D and T2D had more concomitant prevalent diagnoses ($p < 0.0001$). The 10-year incidence rates of all diagnoses were higher among T1D and T2D ($p < 0.0001$), except OA of the CMC-1 joint in men with T1D ($p = 0.055$).

Conclusions CTS, UNE, and possibly also OA of the CMC-1 joint should be included together with TF and DD when referring to ‘the diabetic hand’. The incidence of hand disorders was up to eight times higher among T1D, and both T1D and T2D had more concomitant prevalent diagnoses compared with the population without DM. Future studies should elucidate the pathophysiology behind diabetic hand complications to enable development of effective preventive measures in patients with diabetes.

INTRODUCTION

The concept of hand complications due to diabetes mellitus (DM) was first introduced during the 1970s, although the term ‘the diabetic hand’ did not occur in the literature until much later.¹ Initially, ‘the diabetic hand’ included diagnoses, such as trigger finger

Significance of this study

What is already known about this subject?

- Diabetes has been proposed as a risk factor for common hand disorders, for example, trigger finger and Dupuytren’s disease.
- Less is known regarding the impact of diabetes on osteoarthritis of the hand and compression neuropathies, for example, carpal tunnel syndrome and ulnar nerve entrapment.

What are the new findings?

- All the studied diagnoses in this study were more prevalent among individuals with type 1 diabetes and type 2 diabetes, compared with the population without diabetes.
- The incidence of hand disorders was up to eight times higher among the population with type 1 diabetes compared with the population without diabetes.
- Both population with type 1 and type 2 diabetes had more concomitant prevalent diagnoses when compared with a population without diabetes mellitus.

How might these results change the focus of research or clinical practice?

- The results from this study indicate that complications to diabetes mellitus are common in the hand and many individuals suffer from more than one diagnose.
- Focus should now be on preventative measures against the diabetes epidemic in order to prevent complications such as the diabetic hand.

(TF), limited joint mobility, and Dupuytren’s disease (DD).^{1,2} However, recent publications have suggested that DM is also a risk factor for upper extremity compression neuropathies (CNs), that is, carpal tunnel syndrome (CTS) and ulnar nerve entrapment (UNE),^{3,4} and possibly also osteoarthritis (OA) of the first carpometacarpal (CMC-1) joint.⁵

DM is a growing global health issue, with a prevalence of 420 million people or 9%

globally in 2014,⁶ and 23 million incident cases every year.⁷ Exactly how much higher the prevalences and incidences of the aforementioned diagnoses are among the population with DM is not known, although the number of hand diagnoses is likely to rise in the coming decades due to the increasing prevalence of DM. In order to provide relevant patient information and preventative measures, it is important to clarify how DM complications manifest not only in relation to cardiovascular, renal, or eye complications, but also regarding hand complications, in view of individual suffering as well as costs for society.

Thus, the aim of this study was to further explore prevalences and incidences of CTS, UNE, TF, DD, and OA of the CMC-1 joint among the 1.1 million inhabitants in the region of Skåne in southern Sweden, in persons with or without diabetes, in order to better describe and define the diagnoses associated with 'the diabetic hand'.

RESEARCH DESIGN AND METHODS

Study population

The population studied was all approximately 1.1 million residents living in the region of Skåne in southern Sweden during 2004–2019, aged ≥ 18 years and all registered in the National Diabetes Register (NDR).⁸ The region of Skåne provides healthcare on both primary and specialized secondary care, and there are both public and private caregivers. All caregivers are obliged to register patient diagnoses in the Skåne Healthcare Register (SHR).⁹ Furthermore, there are approximately 50 000 inhabitants in the region with DM, all registered in the NDR.⁸

Data sources

The SHR collects data from all caregivers in the region of Skåne using the unique 10-digit personal identification number assigned to all inhabitants in Sweden. Since 1997, all diagnoses in the region are classified according to International Classification of Disease (ICD) 10; however, the SHR also registers surgical and procedure codes. Furthermore, the SHR registers the type of caregiver (primary care, specialized hospital-based care), age at diagnosis and sex. The register covers the vast majority of all physician visits with an assigned diagnose code and there have been several performed validation studies.⁹

The NDR was founded in 1996 in order to improve treatment and quality of life among inhabitants living with DM in Sweden. In short, the NDR data from all primary and secondary diabetes care in Sweden cover over 90% of all persons with DM in Sweden.¹⁰ The NDR collects data on clinical characteristics, treatments and risk factors, for example, diabetes duration, type of diabetes, medications, glycemic control, blood lipid levels and body mass index (BMI). In this study, only two types of diabetes, that is, type 1 diabetes (T1D) and type 2 diabetes (T2D), were used. The NDR, data collection and definitions of T1D and T2D have previously been described in detail.^{10 11}

Finally, for yearly population data, the Swedish Population Register (<https://www.scb.se/en/>) was used. All three registers were linked using the inhabitant's unique personal identification number.

Case and group definition

All inhabitants in the region of Skåne aged ≥ 18 years, diagnosed with either CTS, UNE, TF, DD, or OA of the CMC-1 joint between 2004 and 2019, were registered in SHR and included in the study. The following ICD-10 codes for respective diagnose were used: CTS: G56.0; UNE: G56.2 G562C, G562D, G562X; TF: M65.3; DD: M72.0; and OA of the CMC-1 joint: M18.0, M18.1, M18.9. Data from both primary and specialized secondary care were used; however, no surgical or procedure codes were used in this study.

Statistical analysis

All calculations were made separately for each of the aforementioned diagnoses and separately for individuals with T1D, T2D, and without DM, thus enabling group comparisons. For prevalence calculation, we only included the inhabitants still alive and living in Skåne on December 31, 2019 who had been diagnosed during 2004–2019. Sex-stratified point prevalence estimates were calculated and analysed; and for group comparison, prevalence ratios (PRs) with 95% CIs, using the Taylor series method, were calculated.¹² For calculation of concomitant prevalent diagnoses (maximum five diagnoses), all individuals with at least one diagnosis were grouped in a dichotomous variable of either one or two or more diagnoses. For comparisons between T1D, T2D, and non-DM groups, the χ^2 test was used.

For incidence calculation, we included inhabitants with first time diagnoses of the respective conditions during the period from 2010 to 2019, without a history of that specific diagnosis during 2004–2009. Age-stratified and sex-stratified incidence ratios (IRs) were calculated and for group comparisons, sex-stratified incidence rate ratios (IRRs) with 95% CI, using the Byar's approximation method, were calculated and analyzed.¹³ When calculating the population at risk, the total number of inhabitants in the region each year from 2010 to 2019 was used, subtracting the number of inhabitants with DM. For population at risk calculation among the population with DM, the total number of individuals with T1D and T2D each year during 2010–2019 was used. The age of each inhabitant as per December 31 of respective year was used when calculating the age-stratified incidence. For incidence calculation, the DM diagnosis had to be established prior to or during the same year as the hand diagnosis. For all calculations, a two-sided p value of < 0.05 was considered significant.

All statistical calculations were made using IBM SPSS statistics for MAC V.27 and Open Epi (www.openepi.com).¹⁴ All figures were made using Microsoft Excel for MAC V.11.5 (Microsoft Corporations, Redmond, Washington, USA).

Table 1 Population demographics as of December 31, 2019 of the inhabitants in region Skåne aged ≥18 years, stratified for diabetes status

Population group (age intervals, years)	Without diabetes	Type 1 diabetes	Type 2 diabetes
Total (18+)	1 041 336	6812	49 395
Women (%)*	528 310 (50.7)	3045 (44.7)	20 453 (41.4)
Total (18+)			
18–29	89 645	577	80
30–39	95 163	426	304
40–49	85 619	486	1020
50–59	84 324	527	2740
60–69	67 723	483	4938
70–79	61 534	409	6955
80+	44 302	137	4416
Men (%)*	513 026 (49.3)	3767 (55.3)	28 942 (58.6)
Total (18+)			
18–29	95 829	684	64
30–39	95 785	550	351
40–49	87 690	653	1470
50–59	84 447	682	4312
60–69	63 790	586	7827
70–79	53 947	508	10 290
80+	31 538	104	4628

*Percentage of sex distribution.

RESULTS

Age-stratified and sex-stratified population demographics as per December 31, 2019 among the inhabitants in Skåne with T1D, T2D, and without DM, respectively, are presented in [table 1](#).

There were in total 551 808 women aged ≥18 years, whereof 3045 with T1D and 20 453 with T2D, and in total 545 735 men aged ≥18 years, whereof 3767 with T1D and 28 942 with T2D.

Prevalence 2004–2019

The prevalence data for CTS, TF, UNE, DD, and OA of the CMC-1 joint, respectively, are presented in [table 2](#), stratified for sex and diabetes status.

The prevalences of all studied diagnoses were higher among the population with T1D and T2D when compared with the population without DM, with PR spanning from 1.8 (95% CI: 1.4 to 2.4, $p < 0.01$) for OA of the CMC-1 joint to 9.4 (95% CI: 8.6 to 10.3, $p < 0.0001$) for TF among women with T1D. [Figure 1](#) presents prevalence data for the respective diagnoses with 95% CI, stratified for sex and diabetes status.

The proportions of the population with a second, concomitant prevalent diagnosis were higher among both individuals with T1D (women 34.0%; 95% CI: 30.6% to 37.5%, men 24.1%; 95% CI: 20.7% to 27.8%) and T2D (women 22.4%; 95% CI: 21.1% to 23.8%, men 18.8%; 95% CI: 17.5% to 20.1%), compared with the population

without DM (women 16.7%; 95% CI: 16.3% to 17.1%, men 13.5%; 95% CI: 13.0% to 14.1%) (X^2 $p < 0.0001$ for all analyses).

IRs 2010–2019

The IRs per 10 000 person-years for CTS, UNE, TF, DD, and OA of the CMC-1 joint, respectively, are presented in [table 3](#), stratified by sex and diabetes status with IRR with 95% CI for group comparison.

The incidence rates were higher for all studied diagnoses in the populations with T1D and T2D when compared with the population without DM, with the exception of OA of the CMC-1 joint among men with T1D (IRR 1.7, 95% CI: 0.9 to 2.8, $p = 0.055$). Trigger finger among women with T1D had the highest IR with 100.5 cases per 10 000 person-years and an IRR of 8.1 (95% CI: 7.1 to 9.1, $p < 0.00001$) compared with the population without DM. Finally, age-stratified and sex-stratified incidence rates for the respective diagnoses in 10-year age groups are presented in online supplemental figures S1–S5.

DISCUSSION

Principal findings

The analysis of the data from the SHR and the NDR from 2004 and 2019 showed markedly higher prevalences of all diagnoses studied, that is, CTS, TF, DD, UNE, and OA

Table 2 Prevalence of the respective hand diagnoses on December 31, 2019 in the population of Skåne aged ≥18 years, stratified for sex and diabetes status between 2004 and 2019

Diagnosis	Without diabetes			Type 1 diabetes			Type 2 diabetes		
	Number of events	Prevalence (%)	Number of events	Prevalence (%)	PR (95% CI)	Number of events	Prevalence (%)	PR (95% CI)	
Carpal tunnel syndrome	18 515	3.5	412	13.5	3.9 (3.5 to 4.2)*	2060	10.1	2.9 (2.7 to 3.0)*	
Ulnar nerve entrapment	2552	0.5	49	1.6	3.3 (2.5 to 4.4)*	278	1.4	2.8 (2.5 to 3.2)*	
Trigger finger	8056	1.6	436	14.3	9.4 (8.6 to 10.3)*	1301	6.4	4.1 (3.9 to 4.4)*	
Dupuytren's disease	1888	0.4	88	2.7	7.5 (6.1 to 9.4)*	249	1.2	3.4 (3.0 to 3.9)*	
OA of the CMC-1 joint	5281	1	55	1.8	1.8 (1.4 to 2.4)*	615	3	3.0 (2.8 to 3.3)*	
Men	Without diabetes			Type 1 diabetes			Type 2 diabetes		
Diagnosis	Number of events	Prevalence (%)	Number of events	Prevalence (%)	PR (95% CI)	Number of events	Prevalence (%)	PR (95% CI)	
Carpal tunnel syndrome	7787	1.5	258	6.8	4.5 (4.0 to 5.1)*	1443	5	3.3 (3.1 to 3.5)*	
Ulnar nerve entrapment	2238	0.4	67	1.8	4.1 (3.2 to 5.2)*	403	1.4	3.2 (2.9 to 3.5)*	
Trigger finger	4241	0.8	247	6.6	7.9 (7.0 to 9.0)*	1083	3.7	4.5 (4.2 to 4.8)*	
Dupuytren's disease	4666	0.9	149	4	4.3 (3.7 to 5.1)*	899	3.1	3.4 (3.2 to 3.7)*	
OA of the CMC-1 joint	1529	0.3	21	0.6	1.9 (1.2 to 2.9)**	287	1	3.3 (2.9 to 3.8)*	

PRs with 95% CI are presented with the population without DM as reference. For population denominator, see table 1.

* $P < 0.00001$, ** $p < 0.01$.

CMC, carpometacarpal; DM, diabetes mellitus; OA, osteoarthritis; PR, prevalence ratio.

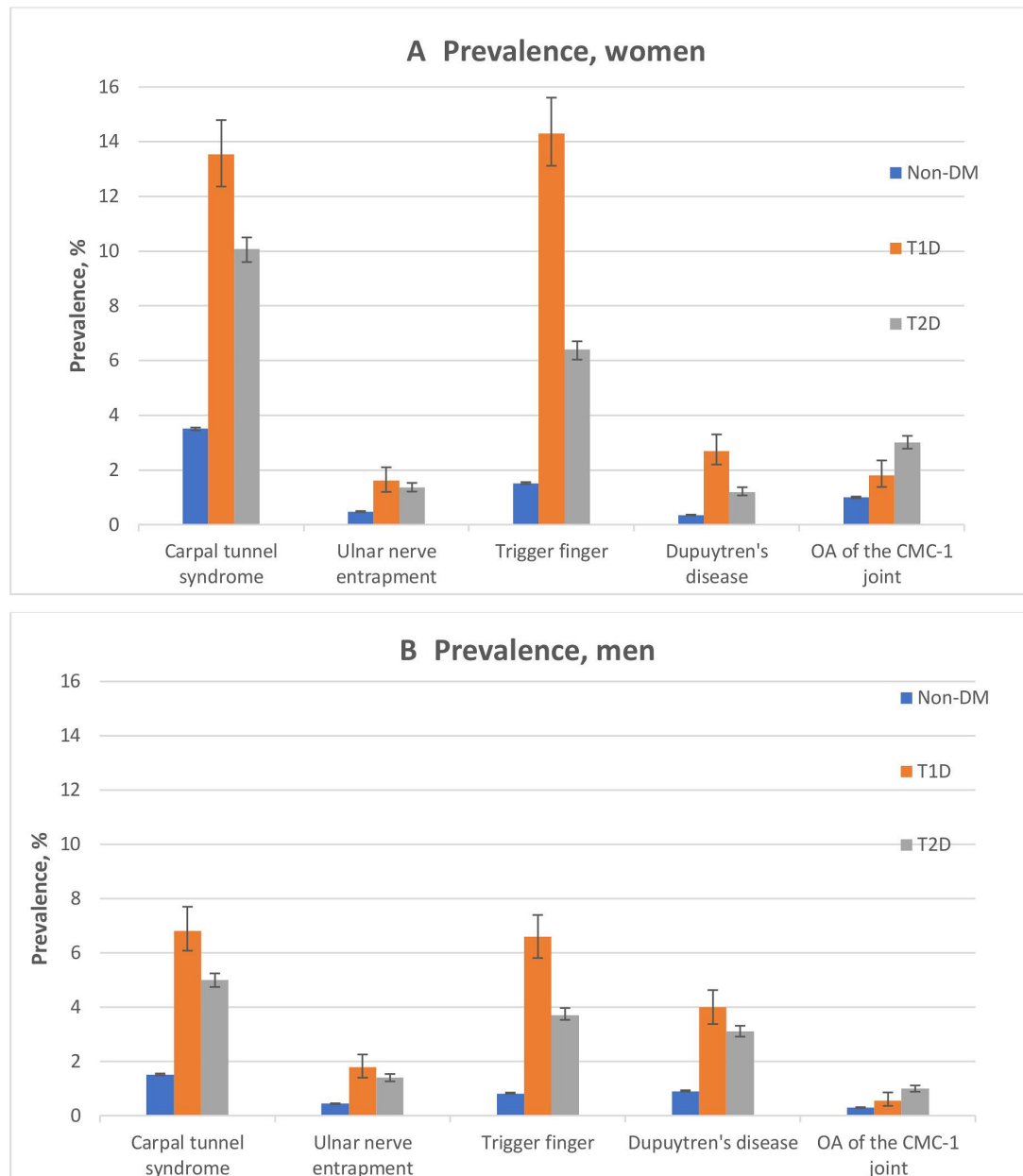


Figure 1 (A,B) Prevalence of hand diagnoses 2004–2019 in the population of Skåne aged ≥ 18 years on December 31, 2019, stratified for sex and diabetes status, presented with 95% CIs. CMC-1, first carpometacarpal; DM, diabetes mellitus; OA, osteoarthritis; T1D, type 1 diabetes; T2D, type 2 diabetes.

of the CMC-1 joint, among both men and women with T1D or T2D, compared with the population without DM.

Furthermore, both populations with T1D and T2D had more concomitant prevalent diagnoses when comparing with the population without DM. Finally, the 10-year incidence of all diagnoses was higher among the populations with T1D and T2D compared with the population without DM, with the exception of OA of the CMC-1 joint among men with T1D. This study adds longitudinal, large-scale population-based data confirming that the entity ‘the diabetic hand’ should include both nerve compression syndromes, such as CTS and UNE, and disorders with impaired range of motion, like TF and DD, and possibly also OA of the CMC-1 joint. Care should be taken when

examining patients with hand problems and concurrent DM, bearing in mind the increased prevalences of all diagnoses in this study in the population with diabetes.

Compression neuropathies

The most common CN in the upper extremity is CTS, followed by UNE.

The present results show that the prevalences of both CTS and UNE are three to four times higher among both the populations with T1D and T2D, compared with the population without DM. These results are in line with several previous studies on DM and CTS.^{15 16} Although the epidemiological data on UNE are scarce, and the number of large cohort studies on UNE is limited,¹⁷ the

Table 3 Incidence rates (IRs, per 10 000 person-years) during 2010–2019 among individuals ≥ 18 years and incidence rate ratios (IRRs) of hand diagnoses among the population with T1D and T2D, respectively, with the population without DM as reference

Diagnosis	Without diabetes				T1D				T2D			
	Number of events	IR/10 000	IRR (ref)	Number of events	IR/10 000	IRR (95% CI)	Number of events	IR/10 000	IRR (95% CI)	Number of events	IR/10 000	IRR (95% CI)
Carpal tunnel syndrome	13 086	26.1	1	250	95.5	3.7 (3.2 to 4.2)*	1007	52.1	2.0 (1.9 to 2.1)*			
Ulnar nerve entrapment	1942	3.9	1	37	14.1	3.7 (2.6 to 5.0)*	145	7.5	1.9 (1.6 to 2.3)*			
Trigger finger	6253	12.5	1	263	100.5	8.1 (7.1 to 9.1)*	813	42	3.4 (3.1 to 3.6)*			
Dupuytren's disease	1648	3.3	1	60	22.9	7.0 (5.4 to 9.0)*	182	9.4	2.9 (2.5 to 3.3)*			
OA of the CMC-1 joint	3711	7.4	1	37	14.1	1.9 (1.4 to 2.6)*	281	14.5	2.0 (1.7 to 2.2)*			
Men	Without diabetes				T1D				T2D			
Diagnosis	Number of events	IR/10000	IRR (ref)	Number of events	IR/10000	IRR (95% CI)	Number of events	IR/10000	IRR (95% CI)	Number of events	IR/10000	IRR (95% CI)
Carpal tunnel syndrome	6178	12.9	1	188	58.1	4.5 (3.9 to 5.2)*	837	31.6	2.5 (2.3 to 2.6)*			
Ulnar nerve entrapment	1715	3.6	1	51	15.8	4.4 (3.3 to 3.8)*	232	8.8	2.5 (2.1 to 2.8)*			
Trigger finger	3662	7.6	1	165	51	6.7 (5.7 to 7.8)*	782	29.5	3.9 (3.6 to 4.2)*			
Dupuytren's disease	3952	8.2	1	119	36.8	4.5 (3.7 to 5.4)*	590	22.3	2.7 (2.5 to 3.0)*			
OA of the CMC-1 joint	1248	2.6	1	14	4.3	1.7 (0.9 to 2.8)**	157	5.9	2.3 (1.9 to 2.7)*			

* $P < 0.00001$, ** $p = 0.055$.

CMC, carpometacarpal; DM, diabetes mellitus; OA, osteoarthritis; T1D, type 1 diabetes; T2D, type 2 diabetes.

findings from this study corroborate both our previous work on identification of risk factors for CN⁴ and electrophysiological studies on UNE.^{3 18}

Several structural and biochemical processes have been proposed as to why CNs are more common among the population with DM. These include deposition of glycated proteins, so called advanced glycation end products (AGEs), in the nerve and surrounding tissue possibly limiting nerve blood supply.^{19 20} Furthermore, nerve swelling and edema due to deposition of intracellular hyperosmotic proteins,³ and alteration of the small microvessels surrounding the nerve,^{21 22} might further decrease the blood supply to the nerve. Finally, biopsies from the posterior interosseous nerve among patients with DM and concurrent CTS have shown a reduction in nerve fiber density compared with controls, indicating a predisposition for nerve compressions among patients with DM.²¹

Taking this together, pathologic structural and biochemical alterations in the peripheral nerve and surrounding tissue due to DM and chronic hyperglycemia might lower the threshold for symptom development when the nerve is compressed, and thus increase the prevalences of CTS and possibly also UNE.⁴

TF and DD

Both TF and DD are considered to be fibroproliferative disorders with alterations in the flexor tendon pulley system²³ and palmar aponeurosis,²⁴ respectively. The exact pathophysiology behind the diagnoses is still not fully understood, especially in the presence of DM.¹ Nevertheless, several biochemical processes have been proposed in earlier studies as to why there is an increased risk of TF and DD among the population with DM. For DD, these include increased deposition of AGEs in the palmar fascia due to hyperglycemia and possible conversion of fibroblasts to myofibroblasts.^{1 25 26} Regarding TF, a similar explanation has been proposed with chronic hyperglycemia leading to glycosylation and collagen deposition in the tendon sheet,¹ possibly thickening the tendon sheet and particularly the A1 pulley. Alterations in collagen degradation due to chronic hyperglycemia have also been proposed.²⁷ However, the number of biochemical studies on TF and DM is to the best of our knowledge very limited, making this issue an obvious target for further research.

The results from our study indicate that the prevalences of both TF and DD are marked higher among both the population with T1D and T2D. Over 14% of the women with T1D had a diagnosis of TF during 2004–2019; an incidence that was eight times higher compared with the population without DM. Similar results were found both among men with T1D and T2D. Our results corroborate several previous studies on the impact of DM on the risks of TF and DD^{26 28–30}; however, our study adds large-scale population-based data supporting that both TF and DD should be included in the concept of ‘the diabetic hand’.

OA of the CMC-1 joint

OA of the CMC-1 joint is a common hand disorder, especially among elderly women. Symptoms include pain and weakness of the thumb, ultimately resulting in loss of function and mobility.³¹ OA has been thoroughly studied in the presence of DM yielding conflicting results, and a potential causal association between the diagnoses is yet to be established.^{5 32–35} Moreover, a BMI has been associated with OA, both of the hip and knee joint, but also with general hand OA and OA of the CMC-1 joint.^{36–38} At the same time, a high BMI is a major risk factor for the development of T2D,³⁹ and also increasingly common among individuals with T1D.⁴⁰

In our study, the prevalences of OA of the CMC-1 joint were higher among both men and women with T1D and T2D compared with the population without DM and, with the exception of men with T1D, the 10-year incidences were also higher among the populations with DM. Nevertheless, due to the observational, retrospective design of our study, we cannot draw any conclusions regarding causality of this finding. Thus, although the prevalence of OA of the CMC-1 joint was slightly higher among both individuals with T1D and T2D, the causal relationship between the diagnoses is still under debate and our results must be interpreted with this in mind.

In future studies aiming to investigate a potential causal link between DM and OA of the CMC-1 joint, BMI and other potential confounding factors that were not available in this study have to be taken into account and adjusted for.³²

Strengths and limitations

The major strength of this study is the large, population-based data on over 1.1 million inhabitants in the region of Skåne. The Swedish 10-digit personal identification number unique for every Swedish citizen, allowing cross-linkage of registries and large-scale epidemiological studies within this region,⁹ makes this study one of the largest epidemiological studies of diabetic hand complications. Another strength is the inclusion of data from primary care as well as from the NDR with nationwide coverage, enabling stratification for T1D and T2D. Studies only including data from specialized, hospital-based care might underestimate the true prevalence of a diagnosis since not all cases are referred from a primary care physician. Our study included diagnoses from both primary care and hospital-based care, thus hopefully coming closer to the true prevalence of the diagnoses. However, our data do only reflect the prevalence and incidence of individuals diagnosed by a physician, and there are undeniably individuals who are only treated by an occupational therapist or do not receive health-care at all for their hand symptoms. With this in mind, our results reflect clinically relevant data compared with studies investigating the prevalence in the general population, for example, survey studies. Furthermore, since all patients had been diagnosed by a physician, the case

validity in our study ought to be high, compared with studies with self-reported data.

Nevertheless, due to the observational nature of the present data, it is important to mention that we are not able to draw any conclusions regarding casual relationships or pathophysiological mechanisms between DM and the diagnoses studied, even though their prevalences indeed were higher both among individuals with T1D and T2D. As previously discussed, there are confounding factors, for example, BMI, that might partly explain the present findings, or actually being a cause to development of, for example, neuropathy, rendering nerves more susceptible to compression.

The reported associations must therefore be interpreted together with previous studies, and meta-analyses would be helpful in order to be able to draw any conclusions regarding the impact of DM on the diagnoses studied.

Moreover, there might be additional diagnoses associated with the diabetic hand. For example, limited joint mobility, which in previous studies have been associated with DM,¹ would have been interesting to be included in this study. Unfortunately, the ICD-10 code for LJT is not as well defined as for the other diagnoses studied, leading to difficulties registering the diagnosis in SHR. A case–control study on patients with T1D and T2D would probably be more suitable for studying LJT in Sweden.

Finally, the study only included data from 2004 to 2019, since the coverage rate of SHR drastically increased in 2004,⁹ and consequently, patients diagnosed before 2004 were not included. Thus, the true prevalence might be higher than described in our data; however, the main results should not have been affected by this. Nevertheless, it is important to mention and should be kept in mind when interpreting the results from our study.

CONCLUSION

The study establishes CTS, UNE, TF, DD, and possibly also OA of the CMC-1 joint to be included in ‘the diabetic hand’ as all aforementioned diagnoses were more prevalent among both populations with T1D and T2D. Furthermore, both populations with T1D and T2D had more concomitant prevalent hand diagnoses when comparing with the population without DM. Future studies should try to elucidate the pathophysiology behind these increased prevalences among the population with DM in order to find potential therapeutic targets enabling prevention of diabetic complications in the hand.

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Contributors The study was designed and planned by MR, MZ, and LBD, and the initial draft of the manuscript was written by MR. All the authors discussed and contributed to intellectual content and to the data interpretation. All the stated authors reviewed and accepted the final version before publishing. MR and LBD are the guarantors of this study.

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Data availability statement Data may be obtained from a third party and are not publicly available. Public access to the data used for this study is limited by the Swedish authorities, however, can be applied for by researchers after contacting the KVB committee in the region of Skåne (www.skane.se/en).

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