Upper extremity impairments in type 1 diabetes in comparison to matched controls without diabetes

- associations to the IGF-system, metabolic factors, disability and
quality of life

Kerstin Gutefeldt

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Linköping 2020

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Printed in Sweden by LiU-Tryck, Linköping, Sweden, 2020

ISBN 978-91-7929-912-5

ISSN 0345-0082

***"Life isn't about waiting for the storm to pass.
It's about learning how to dance in the rain".***

Vivian Greene

To all the people living with diabetes

CONTENTS

CONTENTS	1
ABSTRACT	1
SVENSK SAMMANFATTNING.....	3
LIST OF PAPERS	5
ABBREVIATIONS	6
INTRODUCTION	7
Type 1 diabetes	7
Insulin-Like Growth Factor System.....	7
<i>Growth hormone and IGF-I</i>	7
<i>IGFBP-1 and IGFBP-3</i>	8
<i>Insulin and its impact on the IGF system</i>	8
<i>IGF system in type 1 diabetes</i>	9
Complications in diabetes	10
<i>Microvascular and macrovascular complications</i>	10
<i>Musculoskeletal complications and pathophysiology</i>	10
Disability in type 1 diabetes.....	11
<i>International Classification of Functioning Disability and Health</i>	11
<i>Upper extremity impairments</i>	11
<i>Health-related quality of life (HRQOL) in type 1 diabetes</i>	12
AIMS OF THIS THESIS.....	14
METHODS	15
Overview of the study design, papers I–IV	15
Methods – papers I–III.....	16
<i>Study population and sample, papers I–III</i>	16
<i>Questionnaire - papers I–III</i>	18
<i>Laboratory tests</i>	20
Method - paper IV	21

<i>Study population and samples, paper IV</i>	21
Data analysis	23
<i>Paper I-III</i>	23
<i>Paper IV</i>	23
Ethical approval	23
RESULTS	24
Paper I	24
<i>Prevalence of upper extremity impairments</i>	24
<i>Activity limitations</i>	25
<i>Risk factors</i>	26
Paper II.....	27
<i>Insulin treatment</i>	27
<i>Differences in the GH-IGF-I axis between T1D and controls</i>	27
<i>IGF-I in diabetes</i>	27
<i>Metabolic factors and the IGF system in patients and controls</i>	28
Paper III	30
<i>HRQOL in patients and controls</i>	30
<i>Upper extremity impairments in type 1 diabetes and HRQOL</i>	30
<i>Other risk factors associated with the HRQOL in patients</i>	32
<i>Sick leave in patients and controls</i>	32
PAPER IV	32
<i>Reliability analysis of the questionnaire</i>	32
<i>Self-reported upper extremity impairments</i>	32
<i>Clinical examination of upper extremity impairments</i>	33
<i>Self-reported versus clinical examination of upper extremity impairments</i>	34
DISCUSSION.....	37
Paper I and IV	37
<i>Prevalence of self-reported UEIs</i>	37
<i>Prevalence of UEIs by clinical examination</i>	38
<i>Self-reported UEIs versus clinical impairments and possible key questions</i>	39

<i>Reliability of a self-administered questionnaire</i>	<i>40</i>
<i>UEIs and activity limitation</i>	<i>40</i>
<i>UEIs and risk factors.....</i>	<i>41</i>
Paper II.....	42
<i>Associations between residual endogenous insulin secretion (C-peptide) and the IGF system.....</i>	<i>42</i>
<i>Possible associations between UEIs and the IGF system.....</i>	<i>43</i>
Paper III	43
<i>HRQOL in patients with T1D vs. controls</i>	<i>43</i>
<i>Gender differences</i>	<i>44</i>
<i>HRQOL in patients with T1D and controls with UEIs.....</i>	<i>44</i>
<i>Sick leave in patients with T1D and controls.....</i>	<i>44</i>
Limitations	45
CONCLUSION	46
FUTURE ASPECTS	47
REFERENCES	48
ACKNOWLEDGEMENTS	57

ABSTRACT

Compared with the general population, people with type 1 diabetes (T1D) more often exhibit pathological alterations in musculoskeletal tissue (impairments). Some of these impairments involve the upper extremities, i.e., the shoulders, hands, and fingers. Although present in diabetes, these complications are underdiagnosed and not actively searched for during routine clinical examinations. Furthermore, much is still unclear about these impairments, specifically regarding their etiology, risk factors, and consequences on daily life activities and quality of life. The growth hormone (GH)/insulin-like growth factor (IGF)-system is known to be affected in diabetes, but whether this is involved in upper extremity impairments (UEIs) is unclear. The aim of this thesis was to describe the prevalence of UEIs in patients with diabetes compared with controls. Furthermore, we aimed to search for risk factors of UEIs, and elucidate the impact of UEIs on daily life activities and health-related quality of life (HRQOL).

We used two cohorts; the LedIG cohort (papers I–III), a large population-based study in which all patients with a long duration of T1D (>20 years), aged <67 years, living in the south-east region of Sweden were invited to participate, as well as matched controls without diabetes. This study was based on questionnaires as well as blood samples from the participants. The last paper (IV) included a smaller cohort (n=69) of patients with T1D, who both completed a questionnaire and were the subjects of a clinical examination.

Paper I: The UEIs were common in diabetes, with a prevalence of up to 48%. Hand paresthesia was the most common impairment, followed by shoulder pain and stiffness. The prevalence of UEIs was 2–4 times higher in patients than in controls and was associated with more activity limitations. Risk factors were heterogeneous for the different UEIs and included female sex, increasing age, longer duration of diabetes, and poor glycemic control.

Paper II: The GH-IGF-axis is important for the growth and function of musculoskeletal tissues. We examined differences in the IGF system between patients with T1D on subcutaneous insulin treatment and controls. We found lower levels of IGF-I and insulin-like growth factor-binding protein (IGFBP)-3 and higher levels of GH and IGFBP-1 in patients with T1D than in controls. The largest difference was found in IGFBP-1, and this probably reflected insulin deficiency. The IGF-I levels were increased with increasing insulin doses. However, even at very high insulin doses (>1 U/kg) the IGF-I Z-score was subnormal, indicating that IGF-I cannot be normalized by subcutaneous insulin treatment. Residual endogenous insulin secretion counteracted these alterations.

Furthermore, we investigated possible relationships between UEIs and IGF-I, and found no association.

Paper III: The HRQOL was lower in patients with T1D than in controls. Patients with shoulder impairments, hand paresthesia, and hand stiffness, but not finger impairments, had lower HRQOL scores than patients without these impairments. The patients with T1D showed a higher frequency of sick leave than controls, and a common reason for this was musculoskeletal impairments.

Paper IV: In addition to the self-reported UEIs, the prevalence of UEIs was also investigated by clinical examination. Clinical UEIs were found in 65% of the participants, with shoulder test (hands against back), prayer sign test, and the Phalen's and Tinel's tests being most prevalent. We compared self-reported UEIs to clinical UEIs and found that self-reported impairments were associated with clinical examination. We also found that self-reported shoulder impairments, reduced hand strength, and previous surgery for carpal tunnel syndrome and trigger finger were associated with several other UEIs.

In current diabetic care, there is no established routine to capture UEIs, as opposed to other known diabetes complications. We show that UEIs are more common in patients with T1D than in controls, and that they are related to impaired HRQOL and daily life activity limitations. Clinical routines including self-reported UEIs, e.g. shoulder stiffness and reduced hand strength, might be used to identify patients with UEIs in need of clinical investigation, enhanced preventive and therapeutic strategies, as well as rehabilitative interventions.

SVENSK SAMMANFATTNING

Typ 1 diabetes (T1D) är en kronisk sjukdom som orsakas av att bukspottskörteln genom en autoimmun reaktion förlorar sin förmåga att producera insulin. Insulinbristen gör att sockernivån i blodet stiger och leder också till andra hormonella rubbningar. Orsaken till T1D är fortfarande okänd men man tror att både genetiska och miljömässiga faktorer spelar roll. Näst efter Finland har Sverige den högsta incidensen av T1D i världen. Sedan insulinet upptäcktes i början av 1920-talet har behandlingen av diabetes successivt förbättrats och består idag av regelbundna insulininjektioner eller kontinuerlig insulintillförsel via pump. Höga blodsockerhalter kan på sikt orsaka komplikationer i ögon, njurar, kärl och nerver. Det är också känt att T1D är relaterat till funktionsnedsättningar i övre extremiteten såsom smärta och stelhet i axlar, händer och fingrar samt nedsatt greppstyrka. Målet med avhandlingens delstudier var att undersöka förekomst av och riskfaktorer för dessa symptom vid T1D jämfört med kontroller samt huruvida funktionsnedsättning i övre extremiteten påverkar dagliga aktiviteter och livskvalitet. En annan frågeställning var hur självrapporterad funktionsnedsättning överensstämmer med klinisk undersökning och om man med enkla frågor kan fånga upp riskindivider.

Delstudie I-III baseras på blodprovsanalyser samt postenkät med frågor kring funktionsnedsättning i övre extremiteter, livskvalitet och eventuella begränsningar i dagliga aktiviteter. I denna huvudstudie inkluderades 773 patienter som haft T1D under lång tid (>20 år) samt 708 kontroller. I delstudie IV ingick 69 patienter med T1D som både besvarade enkäter samt undersöktes kliniskt i samband med ordinarie planerade mottagningsbesöket.

Delstudie I visar att funktionsnedsättning i övre extremiteterna är vanliga, med en förekomst på uppemot 48% av enskilda symptom. Funktionsnedsättning var 2 till 4 ggr vanligare vid T1D än hos kontroller och de var relaterade till begränsning i vardagliga aktiviteter. Kvinnligt kön, högre ålder och högre BMI var några predisponerande riskfaktorer för funktionshinder i båda grupperna. Hos individer med T1D utgjorde också blodsockernivån en riskfaktor för axelsmärta och stelhet. **I delstudie IV** fann vi att självrapporterad funktionsnedsättning överensstämde väl med kliniska fynd av funktionsnedsättning i axlar, händer och fingrar. Precis som i delstudie I noterades att funktionsnedsättningarna var mycket vanliga, ofta samexisterade och ofta förekommande på både vänster och höger sida samtidigt. **Delstudie II** visar att IGF-I är signifikant lägre hos individer med T1D än hos kontroller och att kvarvarande förmåga att bilda insulin hos patienter är kopplat till en mer normal IGF-I nivå. Däremot verkar de låga IGF-I nivåerna vid T1D inte vara relaterade till förekomsten av funktionsnedsättning i övre extremiteten. Tidigare studier har kunnat visa att T1D är associerat med nedsatt livskvalitet. Att

leva med diabetes kan av vissa uppfattas svårt till exempel till följd av krävande egenvård eller rädsla för komplikationer. Att uppnå och bevara god livskvalitet utgör ett av de enskilt viktigaste målen för patienten och hälso- och sjukvården. I **delstudie III** visar vi att individer med T1D upplever lägre livskvalitet än kontroller och att detta är starkt relaterat till förekomst av funktionsnedsättning i övre extremiteten. Vi visar även att T1D är associerat med högre sjukfrånvaro jämfört med kontroller och att en betydande orsak till detta är symptom från rörelseapparaten.

I dagens diabetessjukvård uppmärksammas inte funktionsnedsättning i övre extremiteten i lika stor utsträckning som andra diabetesrelaterade komplikationer. Vi visar att funktionsnedsättning i övre extremiteten är betydligt vanligare hos patienter med T1D än kontroller och att de är relaterade till nedsatt livskvalitet och begränsningar i dagliga aktiviteter. Kliniska rutiner med självrapportering av funktionsnedsättning i den övre extremiteten, till exempel axelstelhet och nedsatt handstyrka, skulle kunna användas för att bättre identifiera patienter som behöver ökade preventiva, behandlande och rehabiliterande insatser.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. Upper extremity impairments in type 1 diabetes with long duration; common problems with great impact on daily life.

Kerstin Gutefeldt, Christina A. Hedman, Ingrid S.M. Thyberg, Margareta Bachrach-Lindström, Hans J. Arnqvist and Anna Spångeus

Disability and Rehabilitation (2017) Volume 41, Issue 6, p 633-640

II. Dysregulated Growth Hormone-Insulin-Like Growth Factor-1 Axis in Adult Type 1 Diabetes with Long Duration

Kerstin Gutefeldt, Christina A. Hedman, Ingrid S.M. Thyberg, Margareta Bachrach-Lindström, Anna Spångeus and Hans J. Arnqvist

Clinical Endocrinology (2018) Volume 89, Issue 4, p 424-430

III. Low health-related quality of life is strongly linked to upper extremity impairments in type 1 diabetes with a long duration

Kerstin Gutefeldt, Christina A. Hedman, Ingrid S.M. Thyberg, Margareta Bachrach-Lindström, Hans J. Arnqvist and Anna Spångeus

Disability and Rehabilitation (2020); DOI: 10.1080/09638288.2019.1705924

Published online 6 January 2020

IV. Clinical examination and self-reported upper extremity impairments in patients with long-standing type 1 diabetes mellitus type 1 diabetes

Kerstin Gutefeldt, Simon Lundstedt, Ingrid S.M. Thyberg, Margareta Bachrach-Lindström, Hans J. Arnqvist and Anna Spångeus

Journal of Diabetes Research (2020); DOI: 10.1155/2020/4172635

Published online 11 March 2020

ABBREVIATIONS

AGE	Advanced glycation end-products
ALS	Acid labile unit
CIPII	Continuous Intra-Portal Insulin Infusion
CTGF	Connective tissue growth factor
CSII	Continuous Subcutaneous Insulin Infusion
CIPII	Continuous Intraperitoneal insulin infusion
CVD	Cerebrovascular Disease
GH	Growth hormone
GHRH	Growth hormone releasing hormone
HAQ-DI	The Health Assessment Questionnaire Disability Index
HbA1c	Haemoglobin A1c
HRQOL	Health related Quality of Life
hs-CRP	High sensitivity C-reactive protein
ICD	The International Statistical Classification of Diseases and Related Health problems
ICF	The international Classifications of Functioning, Disability and Health
IGFBP(s)	Insulin-like growth factor binding protein(s)
IGF-I	Insulin-like growth factor-I
IGF-II	Insulin-like growth-factor-II
IGF system	Insulin-like growth factor system
LedIG-cohort	Name of our study cohort (paper I-III)
LJM	Limited Joint mobility
MDI	Multiple Daily injections
SF-36	Short Form Health Survey
T1D	Type 1 diabetes
UEI(s)	Upper extremity impairment(s)

INTRODUCTION

Type 1 diabetes

Type 1 diabetes (T1D) is a chronic disease characterized by a gradual loss of insulin secretion due to an autoimmune attack on the pancreatic beta-cells¹. The triggers behind the immune-mediated attack remains speculative and to date, no cure is available. As T1D is considered a heterogenous disease and genetic vulnerability is almost entirely confined to the immune system, environmental factors are believed to be involved². However, there is still no definitive understanding of its pathogenesis. In Europe, the incidence of T1D has been increasing by more than 3% per year³. Besides Finland, Sweden has the world's highest incidence of T1D, 25–44 per 100 000 per year in children and adolescents⁴. Additionally, the incidence in children in Sweden seems to be increasing with no signs of a plateau⁵.

When insulin deficiency becomes critical, hyperglycemia causes the classic symptoms of increased urination, increased thirst, weight loss, and fatigue, which often lead to the diagnosis of diabetes. With critically low insulin levels, lipolysis cannot be suppressed; thus, the products of fat metabolism, i.e., ketone bodies, accumulate in the bloodstream and if not treated, can cause fatal ketoacidosis⁶.

Usually, some endogenous insulin production persists after the diagnosis but rapidly diminishes within a few years. However, in some individuals, low levels of endogenous insulin secretion can be detected for decades⁷.

The standard treatment for T1D consists of compensating the insulin deficiency with subcutaneous insulin, by multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII). Careful monitoring is needed to prevent acute life-threatening conditions and chronic irreversible organ complications due to hyperglycemia or hypoglycemia⁸.

Insulin-Like Growth Factor System

The insulin-like growth factor (IGF)-system includes 1) IGF-I and IGF-II; 2) the IGF-I and IGF-II receptors; 3) six IGF-binding proteins (IGFBP1–6); and 4) IGFBP proteases. The system plays a crucial role in normal physiology, as well as in pathological conditions such as cell growth, cell repair, and cancer⁹. The IGF-I and II are polypeptides that share many similarities in structure and biological effects, and are structurally very similar to insulin¹⁰.

Growth hormone and IGF-I

Growth hormone (GH) is secreted from the pituitary gland and acts both directly on peripheral tissues and indirectly through the IGF system. The anabolic effects of GH are

mainly mediated by IGF-I. Furthermore, GH directly stimulates osteoblasts and mediates osteoclast turn-over^{11,12}. A GH deficiency thus leads to reduced bone mass, and diminished bone quality and bone mineral density. In addition, GH deficiency contributes to reduced muscle mass and strength and increased fat deposition¹³. In an opposite situation, such as in acromegaly (abnormal GH-secretion due to a pituitary tumor) the musculoskeletal tissues become enlarged and edematous¹⁴.

The IGF-I is mainly produced by the liver and its receptors are expressed in nearly all human tissues, except mature adipocytes and hepatocytes¹⁵. Furthermore, IGF-I is regulated by GH and mediates the anabolic actions of GH both systemically and in a para/autocrine fashion. In addition to GH, IGF-I is also influenced by age, insulin, food intake, and sex hormones. Moreover, IGF-I promotes growth in children and adolescents, cell differentiation, and has cell protective effects. It is essential for musculoskeletal structure and probably also exerts effects on cardiovascular function⁹. Both IGF-I and GH are involved in glucose metabolism^{10,16}, where they seem to have opposite effects. While IGF-I increases insulin sensitivity, GH promotes insulin resistance^{17,18}.

IGFBP-1 and IGFBP-3

According to the hypothesis of free hormones, the IGFBPs modulate the bioavailable fraction of IGF-I (free IGF-I)¹⁹. Circulating IGF-I is bound to IGFBPs and less than 1% is free and bioactive²⁰. Free IGF-I is regulated within hours by IGFBP-1 produced in the liver²¹. As the most important inhibitor of IGF-I-mediated actions, IGFBP-1 is strictly inhibited by insulin^{20,22}. Furthermore, IGFBP-1 has been proposed a marker for insulin deficiency and sensitivity^{21,23,24}.

IGFBP-3 is the major carrier protein of IGF-I (binds 90-96% in serum)²⁵ and stores IGF-I in a ternary complex composed of IGF-I, IGFBP-3, and the acid labile subunit (ALS). This ternary complex is restricted to the circulation²⁶. Moreover, IGFBP-3 is synthesized by the liver and stimulated by GH in a direct manner. Age and nutrition are two important factors that determine serum IGFBP-3 levels. Testosterone, estrogen, and thyroxine also correlate positively with IGFBP-3 levels²⁷.

Insulin and its impact on the IGF system

Under normal physiological conditions, insulin produced by the pancreas reaches the liver directly through the portal vein, thereby exposing the liver to much higher concentrations of insulin than the rest of the body²⁸. Insulin enhances the synthesis of IGF-I in the liver, probably by increasing the expression of GH-receptors²⁹ (Figure 1). Insulin also increases the bioavailability of circulating IGF-I by inhibiting the synthesis of IGFBP-1²¹.

Endogenous insulin secretion can be evaluated by measuring levels of C-peptide, which is released at the same time as insulin but remains measurable in the bloodstream for a longer period of time³⁰.

Current available treatment strategies for T1D are not physiological as insulin is administered subcutaneously and not directly to the portal vein. This probably results in portal insulin deficiency, which may affect insulin-mediated processes in the liver. One current theory is that intraportal insulin deficiency might explain the altered IGF system observed in T1D.

Figure 1. Insulin (via the portal vein) upregulates growth hormone receptors (GHR) and thereby increases growth hormone (GH) sensitivity in the liver, which increases insulin-like growth factor I (IGF-I) production. Insulin directly suppresses insulin-like growth factor-binding protein 1 (IGFBP-1) production in the liver at the transcription level. GH increases insulin secretion mainly by inducing insulin resistance. ALS, acid labile subunit.

IGF system in type 1 diabetes

In T1D, low IGF-I bioactivity, due to reduced IGF-I levels and increased IGFBP-1 levels, leads to diminished negative feedback on the pituitary gland, and generates GH hypersecretion (Figure 1). The IGF-I levels are typically low despite increased secretion of GH in T1D and is suggestive of GH resistance³¹. Earlier studies indicate that even if blood glucose is normalized with subcutaneous insulin treatment, the IGF system still remains impaired³². Continuous intraperitoneal insulin infusion (CIPII) treatment tends to normalize the alterations in the IGF system in T1D³³, probably because of enhanced insulin absorption into the portal vein. A study by Hedman et al.³² showed an association between C-peptide and circulating IGF-I levels, suggesting that insulin levels in the vena portae are important for IGF-I levels in T1D.

Complications in diabetes

Microvascular and macrovascular complications

Patients with T1D can develop serious microvascular and macrovascular complications, due to hyperglycemia, including retinopathy, nephropathy, neuropathy, and cardiovascular disease³⁴. The prevalence of severe retinopathy has been estimated to be 30% and is reportedly related to age at the onset of diabetes³⁵. Two well established risk factors for retinopathy are glycemic control and duration of diabetes³⁶. Since the hemoglobin A1c test (HbA1c) became available in 1980, (as an estimate of blood glucose control over the previous 6–8 weeks) it has become evident that glycemic control is strongly correlated with these complications. The possible role of the GH-IGF-axis in diabetic angiopathy has been hypothesized and explored, but the results of several studies have been inconclusive^{37–41}.

Musculoskeletal complications and pathophysiology

Musculoskeletal disability was described in the 1950s by Lundbaek et al.⁴². However, the pathophysiology of the musculoskeletal upper extremity impairments (UEIs) seen in T1D is still not fully understood but is probably multifactorial. Several studies have associated UEIs with age and diabetes duration^{43,44}. Whether glycemic control is involved in the pathogenesis of UEIs is more controversial⁴⁵. Some previous reports have also shown a relationship between UEIs and other diabetes complications such as neuropathy, macrovascular disease, and even mortality^{44,46}.

In addition to its mitogenic effects, IGF-I is thought to be an important regulator of connective tissue metabolism, which is also affected by the diabetic state; thus, low IGF-levels could potentially play a part in the development of UEIs¹⁶. Interestingly, fibromyalgia, which is characterized by muscle pain, has been associated with low IGF-levels and has thus been compared with GH deficiency⁴⁷. To date, UEIs related to T1D have not gained much attention in clinical diabetes care. Previous smaller studies on connective tissue complications in diabetes usually combine T1D and T2D, and most studies do not include control groups^{48,49}. Studies in patients with T1D and UEIs and a possible association with the IGF system are lacking. Amin et al.⁵⁰ found an association between limited joint mobility (LJM) and low IGF levels. As far as we know, that was the only previous study to have addressed this subject.

To our knowledge, only one previous study has addressed the possible role of inflammation in the UEIs associated with diabetes. Bridgman et al.⁵¹ investigated erythrocyte sedimentation in diabetic patients with frozen shoulder; however, they found no significant differences.

One proposed hypothesis is that of advanced glycation end products (AGEs), which cross-link the connective tissue^{44,52}. The AGEs seem to accumulate in all individuals with increasing age⁵³; however, this process seems to be accelerated in diabetes⁵⁴. The alterations observed in diabetic tissue (which becomes thicker and stiffer) may be more sensitive to trauma. The AGEs are also involved in the processing of reactive oxygen

products, which could lead to an inflammatory state⁵⁵. Higher AGE concentrations (measured by skin intrinsic fluorescence) have been reported in individuals with UEIs^{44,56}.

Disability in type 1 diabetes

International Classification of Functioning Disability and Health

The terminology proposed by the International Classification of Functioning Disability and Health (ICF) in 1980, and approved by the World Health Organization to define disability has been adopted for the purposes of this thesis⁵⁷. The ICF includes a terminology and classification system for disabilities, which can be used to describe disabilities related to a certain disease, as defined by the International Statistical Classification of Diseases and Related Health problems (ICD). The ICF terminology constitutes a scientific base for communicating health-related states between health care workers and researchers⁵⁸. The ICF defines disability as impairment in body function or structure, as well as activity limitation or participation restriction (Figure 2).

Figure 2. The International Classification of Functioning, Disability, and Health to describe disabilities as impairments, activity limitation, and participation restrictions in type 1 diabetes.

Upper extremity impairments

Hand stiffness, later referred to as LJM was described as early as the 1950s by Lundbaek et al.⁴². However, according to the literature, these impairments initially did not receive a lot of attention until interest was revived by Rosenbloom et al.⁵⁹, who described LJM in children with diabetes in the 1970s. The authors described connective tissue alterations, including in the upper extremities of adolescents with insulin-

dependent diabetes. In current clinical diabetes care, connective tissue alterations are still not acknowledged to the same extent as microvascular and macrovascular complications.

Musculoskeletal manifestations are common in patients with T1D⁴⁴ and earlier studies indicate that diabetes is associated with UEIs measured by mobility and physical strength^{44,60,61}. It is mainly the periarticular tissue around shoulders, as well as the hands and fingers that are affected⁶². Stenosing tenosynovitis (trigger finger), carpal tunnel syndrome, LJM, Dupuytren's contracture, and adhesive capsulitis (frozen shoulder) are all conditions that are more prevalently observed in patients with diabetes^{45,62}.

Adhesive capsulitis (Frozen shoulder) is a condition characterized by painful restriction in shoulder movement. Abduction and external rotation are mainly affected^{44,45,63}. Frozen shoulder is a progressive condition, with a duration of 2–3 years. It is characterized by three defined stages, including pain, increasing stiffness, and finally relieved symptoms (recovering phase). Carpal tunnel (CT) syndrome is characterized by progressive compression of the median nerve within the carpal tunnel, causing a tingling paresthesia and/or loss of sensation in the radial portion of the hand, and often affecting sleep^{64,65}.

The LJM refers to an inability to extend the fingers in the metacarpal and interphalangeal joints, which can be demonstrated by the "prayers sign". The alterations are often bilateral and initiated in the fifth finger⁶². Flexor tenosynovitis (trigger finger) is characterized by a proliferation of fibrous tissue in the tendon sheath of the finger(s). Alterations prevent the smooth movement of the tendon through the sheath, causing a finger locking phenomenon in a flexed or extended position⁶². Dupuytren's contracture is a fibrous process of the palmar fascia that makes it thicker and shorter. The fibrous fascia prevents full extension of the affected digits⁶².

Health-related quality of life (HRQOL) in type 1 diabetes

Physical and mental impairments, activity limitations, and participation restrictions as defined by the ICF are often included in questionnaires aimed to assess the HRQOL⁶⁶. Lower HRQOL scores have been reported in patients with diabetes^{67,68}. The inclusion of HRQOL scores in health care has become an increasingly important aspect of medicine^{68,69}. As treatments become more expensive, medical efficiency is more thoroughly evaluated as a tool for the allocation of health care resources; thus, the HRQOL is an important factor. Furthermore, psychosocial well-being seems to be crucial to achieving successful diabetes care⁷⁰.

A diagnosis of T1D usually leads to a personal crisis. It is a chronic disease, and to date, no cure is available. It involves constant monitoring of blood glucose levels and the administration of insulin via MDI or CSII. Polonsky et al.⁷¹ summarizes three crucial reasons why health care providers should be concerned about HRQOL. Firstly, individuals with diabetes experience a diminished HRQOL⁷². Secondly, the patients' perceived HRQOL is the most important outcome clinically and in research. Thirdly, psychosocial issues determine the patients' ability to cope with diabetes self-care issues⁷³. Diabetes

has been associated with depression^{74,75}. The fear of complications might also have considerable impact on the individuals affected^{68,76}.

Some authors propose that the HRQOL in patients with diabetes should be evaluated with both generic and disease-specific questionnaires. Furthermore, a distinction should be made between health status and quality of life, that is, if an individual perceives that they are in poor health, they might report a diminished HRQOL. However, if an individual perceives that their health status is excellent, the HRQOL might still be impaired⁷⁷.

Reports regarding the possible impact of UEIs on the perceived HRQOL in patients with T1D are few⁷⁸. Interestingly, a previous study indicated that the most common cause for disability in diabetes can be explained by mental and musculoskeletal disorders, which is why we found it important to investigate these observations further⁷⁶.

The magnitude of physical and mental disabilities in patients with long-standing diabetes has received very little attention compared with other known long-term complications. There is a great need for increased knowledge about disabilities in T1D compared with disabilities in controls. Questions can also be raised regarding possible needs, to identify patients with consistent disabilities who may possibly be in need of further interventions.

AIMS OF THIS THESIS

The general aims of this thesis were to describe prevalence of UEIs in diabetes patients in comparison to controls, to search for risk factors for UEI, and to elucidate how the UEIs impact on daily life activity and HRQOL.

Specific aims:

- To describe prevalence of UEIs in T1D patients with long duration compared to controls without diabetes (**Paper I**).
- To investigate if reported UEIs are associated with activity limitations in T1D patients in comparison to controls without diabetes (**Paper I**).
- To explore possible risk factors associated with UEIs (**Paper I and II**).
- To examine differences in GH-IGF-I axis between T1D patients on subcutaneous insulin treatment and controls without diabetes (**Paper II**).
- To explore associations between IGF-I and exogenous insulin and residual endogenous insulin secretion (C-peptide), respectively, in T1D patients (**Paper II**).
- To compare HRQOL and frequency of sick-leave in T1D patients with controls without diabetes (**Paper III**).
- To investigate HRQOL in T1D patients reporting UEIs compared to those who do not report UEIs (**Paper III**).
- To describe prevalence of clinically confirmed UEIs in T1D patients (**Paper IV**).
- To investigate the relation of self-reported impairments to clinical findings, and whether key-questions of risk individuals for UEIs could be identified (**Paper IV**).
- To investigate if answers to our self-reported questionnaire regarding UEIs are reliable (**Paper IV**).

METHODS

Overview of the study design, papers I–IV

A comprehensive description of the study design and methods are shown in Table 1. Papers I–III were focused on the LedIG cohort, and paper IV was focused on a clinically investigated cohort.

Table 1. Overview of all four papers

Study design and Setting	Data collection method	Participation
Paper I Cross-sectional, observational study South-east region of Sweden	Analysis of blood samples and self-administered questionnaires (including HAQ and questions on UEIs).	LedIG cohort: Patients n=773 (females 55%) Mean age, 50±10 years Controls n=708 (females 61%) Mean age, 54±9 years Blood samples Patients n=603, Controls n=531
Paper II Cross-sectional, observational study South-east region of Sweden	Analysis of blood samples and self-administered questionnaires (including questions on UEIs).	LedIG cohort (only those with blood samples): Patients n=605 (females 56%) Mean age, 51±9 years Controls n=533 (females 62%) Mean age, 55±9 years
Paper III Cross-sectional, observational study South-east region of Sweden	Self-administered questionnaires (including SF-36 and questions on UEIs).	LedIG cohort: Patients n=773 (females 55%) Mean age, 50±10 years Controls n=708 (females 61%) Mean age, 54±9 years
Paper IV Cross-sectional, observational study Linköping University Hospital	Self-administered questionnaires, part 1 section on musculoskeletal symptoms in addition to laboratory data (from medical records) and a clinical examination.	Clinical cohort: patients n= 69 (females 51 %) Mean age, 45±14 years

HAQ=Health Assessment Questionnaire; UEIs=upper extremity impairments; SF-36=Short Form (36) Health Survey.

Methods – papers I–III

Study population and sample, papers I–III

Overall, this was a population-based cross-sectional observational study; a design suitable when investigating the prevalence of disease in different populations. The study was conducted in cooperation with all nine hospitals in the south-east region in Sweden between 2010 and 2013. All patients with T1D were recruited using the local diabetes registers of the hospitals. In Sweden, almost everyone with T1D are cared for at hospital outpatient diabetes clinics. Therefore, our recruitment from all nine hospitals probably included almost all patients with T1D in the south-eastern region. Exclusively, patients with T1D were included and fulfilled the following three criteria: 1) onset of diabetes before the age of 35 years; 2) maximum age of 67 years; and 3) diabetes duration >20 years. The reasons for our inclusion criteria were as follows: before the age of 35 years, T1D is the major type of diabetes. A long diabetes duration i.e., >20 years seemed feasible to include patients with developed diabetes-related complications, in whom endogenous insulin secretion would have ceased. Furthermore, the age criteria of a maximum of 67 years was set to avoid age-related UEIs.

Patients matching the criteria were invited to participate. The intention of these inclusion criteria was to get the largest sample size possible. No exclusion criteria were used, as we believed exclusion of subjects due to other accompanied diseases or impairments could introduce bias in the normal variation present in the diabetic population.

The controls, matched for sex and age ± 5 years, were selected from the Swedish population registers and invited by a letter in the mail when the respective patients were included in the study. All controls who reported a history of diabetes or had an elevated fasting plasma glucose level of ≥ 7 mmol/L⁷⁹ were excluded.

Patients and controls received an invitation letter, including an extensive questionnaire. The questionnaires were identical, except for diabetes-specific questions, and was composed of four distinct parts. All participants (patients and controls) were also asked to leave fasting blood samples at their local primary care centre or hospital depending on their place of residence.

Of all the patients with T1D fulfilling the inclusion criteria in the south-eastern region (n=1727), 773 agreed to participate. A total of 721 matched controls also agreed to participate (n=1995, invited). In the control group, 13 were excluded because of fasting plasma glucose levels of ≥ 7 mmol/L; finally, 708 controls remained in the study. Hence the response rate was 45% in patients and 36% in controls.

We performed a drop-out analysis of patients, which showed that dropouts were younger and had a higher proportion of male patients. The characteristics of both patients and controls comprising the study population are summarized in Table 2.

Table 2. Characteristics of patients and controls in papers I-III

	Patients	Controls	Patients		Controls	
	All	All	Female	Male	Female	Male
Questionnaire (number)	773	708	421	352	431	277
Female subjects (%)	55	61*				
Age (years)	50±10	54±9*	50±10 ^a	51.0±9.6 ^b	53±10 ^{ad}	56±9 ^{bd}
BMI (kg/m ²)	26.3±4.1	26.0±3.9	26.3±4.3 ^a	26.1±3.9	25.6±4.1 ^{ad}	26.6±3.4 ^d
Diabetes duration (years)	35±10		36±10 ^c	34±9 ^c		
Current smoker (%)	10	11	11	8.5	11	10
Celiac disease (%)	3	1*	4 ^a	3	1 ^a	1
Previous Cardiovascular event (%) [†]	11	4*	7 ^{ac}	14 ^{bc}	3 ^{ad}	6 ^{bd}
Previous myocardial infarction (%)	5	2*	4 ^a	7	1 ^{ad}	4 ^d
Angina pectoris (%)	7	2*	7 ^a	7 ^b	1 ^a	3 ^b
Previous stroke (%)	3	2	2	3	1	2
Retinopathy (%) [‡]	39		36	42		
Blood samples (number)	603	531	338	265	331	200
HbA1c (mmol/mol)	65±11		64±10	65±12		
HbA1c (%)	8.1±1.0		8.0±0.9	8.1±1.1		
CRP (mg/L)	1.0(0.3-2.7)	0.8(0.3-2.1)*	1.1(0.3-3.2) ^a	0.8(0.3-2.3)	0.8(0.3-2.4) ^a	0.8(0.3-2.0)
GFR (mL/min/1.73 m ²)	85.9±19.5	88.5±13.0*	83.4±19.2 ^{ac}	89.1±19.5 ^c	88.9±13.3 ^a	87.8±12.6

Data are presented as mean±SD. *= $P < 0.05$ for T1D vs. control. Letters a–d denote significance ($P < 0.05$) when analysis was performed separately for gender; a=type 1 diabetic female vs. control female; b=type 1 diabetic male vs. control male; c=type 1 diabetic female vs. type 1 diabetic male; d=control female vs. control male. [†]Previous myocardial infarction, angina, and/or stroke. [‡]Retinopathy defined as self-reported history of laser treatment to either of the eyes. BMI=body mass index; HbA1c=hemoglobin A1c test; CRP=C-reactive protein; GFR=glomerular filtration rate.

The mean age of the patients was 50±10 years and the mean diabetes duration was 35±10 years. There were more women than men who agreed to participate (55% vs. 45%). The controls were slightly older than the patients, as their mean age was 54±9 years, and they comprised more female participants (61%). The mean age at the onset of diabetes (LedIG cohort) was 15±9 years (Figure 3).

Figure 3. LedIG-cohort, mean age at onset of diabetes.

Questionnaire - papers I–III

The self-administered questionnaire was sent to all participants by post. Another posted reminder was sent if no response was received. In cases for which patients had completed the questionnaire but had not donated blood samples, a reminder by telephone was given. The contents of the questionnaire were identical for patients and controls, except for diabetes-specific questions, as described below.

Part 1: Upper extremity impairments (UEIs)

The first part of the questionnaire was study-specific and was developed by the research group in collaboration with the Rheumatology Department at Linköping University Hospital. It included background data such as diabetes-related complications and type and dosage of insulin. Furthermore, it included 12 questions regarding symptoms manifested in the upper extremities (Table 3).

In order to handle our data on UEIs, we constructed proxy variables representative of five previously defined impairments. These impairments included:

1. *Shoulder impairment*=shoulder pain AND stiffness (questions 1 and 2) - proxy for frozen shoulder
2. *Hand stiffness* (question 4) - proxy for LJM
3. *Hand paresthesia*=tingling or loss of sensation/numbness and/or awaken at night because of pain or tingling/loss of sensation in the hands (questions 5 and/or 6) - proxy for CT
4. *Finger locking* (question 9) - proxy for trigger finger
5. *Flexed finger* (question 12) - proxy for LJM/Dupuytren's contracture

Table 3. Overview of the 12 questions (UEIs)

Questionnaire	
1.	Do you have pain/aches in the shoulder joints? (Shoulder pain)
2.	Do you have stiffness in the shoulder joints? (Shoulder stiffness)
3.	Do you have pain/aches in the hand or forearm? (Hand pain)
4.	Are you stiff in the hand or forearm? (Hand stiffness)
5.	Do you have tingling or a loss of sensation/numbness in the fingers? (Hand tingling-numbness)
6.	Do you awaken during the night because of pain or tingling/loss of sensation in the hands? (Wake up to tingling fingers)
7.	Do you experience weakness in the hand? (Reduced hand strength)
8.	Have you ever had surgery for carpal tunnel syndrome (nerve entrapment in the wrist)? (Previous CT surgery)
9.	Does any finger lock when trying to bend it? (Finger locking)
10.	Do you have tendon nodules in the palm of either hand? (Hand nodules)
11.	Have you ever had surgery for tendon nodules or a stricture in the tendon sheath of the palm? (Previous TF surgery)
12.	Have you any trouble straightening your finger/fingers? (Flexed finger)

CT=Carpal tunnel syndrome, TF=Trigger finger

Part 2: The Health Assessment Questionnaire - Disability Index (HAQ-DI)

Part 2 contained the self-administered validated HAQ-DI, which was used to study activity limitation. The HAQ-DI was originally developed and validated in the discipline of rheumatology in the 1980s. It has been translated and is recognized worldwide in a broad range of chronic conditions, including diabetes⁸⁰⁻⁸². The HAQ-DI is composed of 20 questions divided into eight categories. It was set to determine the activities of daily life, including 1) dressing, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) other common daily activities. For each category, there was a scale with four levels of performance graded 0–3; where 0=no difficulty; 1=some difficulty; 2=much difficulty; and 3=unable to do. The highest score from each category was recorded and used to calculate the mean of all eight categories, i.e., the HAQ score. A score ranging from

0–1 was interpreted as mild to moderate; 1–2, moderate to severe; and 2–3, severe difficulty in performing daily activities.

Part 3: Health related quality of life-Short-Form General Health Survey (SF-36)

In this study, we used the validated Swedish SF-36 as the outcome measure for the HRQOL⁸³. The SF-36 is a questionnaire comprising 36 questions, which is used to evaluate the individual's health status in a multi-dimensional fashion. Its content covers a broad range of physical, mental, and social well-being perceptions to derive a more personal estimate of perceived health⁸³. It is considered to be one of the most extensively used generic measures of the quality of life and is thought to be most suitable when comparing the HRQOL of patients with illness with those who present no illness⁶⁸.

The SF-36 contains an eight-item scale of the following: physical functioning (SF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). In summary, the SF-36 comprises both physical and mental aspects, including function, well-being, disability, and personal evaluation.

The SF-36 gives a total score for each of the eight subscales. The subscales include 2–10 subqueries with 2–6 possible answers, depending on the item scale. The scoring is calculated in several steps and requires the use of various tables in the SF-36 manual^{83,84}. In the manual, there are specific questions that belong to each subscale. Some questions require reversed scoring and the number of points for each question differs. Regarding how each subscale is scored, when initial scores have been recorded, the final scores for each dimension are added together. The scores for each subscale are finally transformed into a score ranging from 1–100. Higher scores consistently indicate a better perceived quality of life. Our calculations were performed using software with appropriate preprogrammed algorithms.

Laboratory tests

After an overnight fast, blood samples were collected by venipuncture at the local hospitals. The samples were analyzed at the Department of Clinical Chemistry, Linköping University Hospital. The laboratory is accredited by SWEDAC (Swedish Board for Accreditation and Conformity Assessment). Serum samples for the specific measurements listed in Table 4 were stored at -80 °C until further analysis. High sensitivity C-reactive protein (hs-CRP), P-creatinine, HbA1c, and plasma glucose were analyzed using routine methods. The methods used for the analyses of IGF-I, IGFBP-1, IGFBP-3, GH, and C-peptide are described in Table 4. The IGF-I Z-scores were calculated using the methods described by Elmlinger et al.⁸⁵.

Table 4. Overview of specific blood sample analyses in paper II

Blood sample	Method
IGF-I	IGF-I was measured by a solid-phase, enzyme-labeled chemiluminescent immunometric assay (IMMULITE 2000 immunoassay system, Siemens Healthcare Diagnostics)
IGFBP-1	IGFBP-1 was measured in the serum using a commercial one-step ELISA kit (R&D Systems, Minneapolis, MN, USA)
IGFBP-3	IGFBP-3 was measured using the IDS-iSYS IGFBP-3 assay, an automated chemiluminescence immunoassay provided by Immunodiagnostic Systems Ltd (IDS, Boldon Business Park, Boldon, Tyne & Wear, England)
GH	Growth hormone was analyzed using the immunoassay, Elecsys hGH assay on Cobas® (Roche Diagnostics Ltd, Rotkreuz, Switzerland)
C-peptide	C-peptide was analyzed using the Mercodia Ultrasensitive C-peptide ELISA® kit (Mercodia AB, Uppsala, Sweden)

IGF=insulin-like growth factor; IGFBP=insulin-like growth factor-binding protein; ELISA=enzyme-linked immunosorbent assay; GH=growth hormone.

Method - paper IV

Study population and samples, paper IV

As the UEIs in studies I–III were self-reported, we also aimed to analyze the UEIs in a clinical setting. Patients with T1D who attended the outpatient diabetes clinic at Linköping University Hospital were invited to participate during 2017 and 2018.

In this study, the inclusion criteria were T1D and an age from 18–69 years. Patients were sent invitations through the post, along with a questionnaire regarding UEIs and a consent form. In cases of agreement, the signed consent form together with the questionnaire were returned to the clinic.

A clinical examination was performed close to the routine planned visit to the clinic. Before the clinical examination, patients were asked to complete the questionnaire a second time. The examination was performed by two investigators trained by a physiotherapist and an occupational therapist specialized in examination techniques for the upper extremities. To be able to compare the questionnaire with clinical examination, the examination followed a protocol (designed by the research group) that was directly related to the items of the questionnaire. Background data, such as present diabetes complications and laboratory data of the HbA1c and urine albumin (to assess microalbuminuria or macroalbuminuria) levels, were collected from medical records.

In Table 5, the characteristics of the patients are presented. Altogether, 69 patients participated in the study out of 200 who were initially invited. Approximately half were female patients. No drop-out analysis was conducted.

Table 5. Characteristics of patients in study IV.

	Patients
Number	69
Females (%)	51
Age (years)	45±14
BMI (kg/m ²)	27±5
Diabetes duration (years)	26±15
HbA1c (mmol/mol)	59±12
Retinopathy (%) [#]	35
Nephropathy (%) [¶]	9
Cardiovascular disease (%) [§]	6
Neuropathy (%) [‡]	29

#Retinopathy defined as laser-treated retinopathy to either of the eyes. **¶Nephropathy** defined as microalbuminuria or macroalbuminuria. **§Cardiovascular disease** (previous stroke, myocardial infarction/angina or present peripheral arterial disease). **‡Neuropathy** defined as impaired sensibility tested by monofilament (10 g) and vibration (tuning fork 128 Hz). BMI=body mass index; HbA1c=hemoglobin A1c test.

Questionnaire paper IV

The questionnaire sent to the patients contained the same 12 questions on UEIs used previously in papers I–III (Table 3).

Test-retest analysis

To conduct the reliability analysis of self-reported impairments, we compared the participants answers from the first questionnaire to the answers of the second questionnaire. If the item (answer) obtained in the first questionnaire was equal to the corresponding item in the second questionnaire, it was considered an agreement.

Clinical examination test

The clinical investigation was performed using a study-specific protocol (designed by the research group). All clinical tests are described in detail in paper IV (methods section) and were directly related to the 12 questions described above. All clinical tests were performed on all 69 patients on both sides (left and right), regardless of previous self-reported impairments. A positive clinical test result (categorical variables) was defined as either positive or negative i.e., 0=not found; 1=positive on one side; and 2=positive on both sides. All tests were performed once on each arm, with the exception of shoulder mobility measurements (using a goniometer), which were recorded twice for

each shoulder. The calculated mean of the two values was recorded. Grip force was also evaluated in all patients on both left and right sides.

Data analysis

Paper I-III

Parametric tests were used, which we considered appropriate in the relatively large study samples with a normal distribution. The Student's t-test was used for continuous variables, when comparing two groups and ANOVA using Bonferroni correction was used as the post hoc test if three or more groups were included in the analysis. The chi-squared test was used for categorical variables, and univariate and multiple regression models when analyzing UEIs in relation to risk factors (paper I) and the HRQOL (paper III), as well as the IGF-I Z-score in relation to the IGF system and metabolic factors (paper II). Our UEIs were set as dependent variables. The risk factors were set as independent variables in paper I, as well as the eight SF-36 dimensions in paper III and the IGF-I Z-score in paper II.

The levels of Hs-CRP (paper I), GH, and IGFBP-1 (paper II) all showed a skewed distribution, and were thus log-transformed before statistical analysis was performed.

Paper IV

The patient characteristics (with or without UEIs) were compared using the independent t-test for numerical variables and the chi-squared test for categorical variables. In order to investigate the reliability of self-reported impairments, we used descriptive statistics (frequency), and thus obtained the percentage agreement of each item in the questionnaire. Pearson's correlation was used to investigate the relationship between clinical findings and self-reported impairments. Regarding acknowledged gender differences in grip force⁸⁶, we decided to analyze male and female patients separately. The first completed questionnaire was used to compare the results of the self-reported impairments with those of the clinical findings.

All statistics were calculated using the SPSS 23.0 for Windows software (IBM Statistics, New York, USA).

Ethical approval

A signed informed consent form was obtained from all participants. The Research Ethics Committee of the Faculty of Health Sciences, Linköping University approved the study (M245-09:2010-03-17 and 2017/72-32).

RESULTS

Paper I

Prevalence of upper extremity impairments

The prevalence of shoulder, hand, and finger impairments was 2–4 times higher in patients compared with controls, which was statistically significant for all investigated impairments (Figure 4)⁸⁷. One in five patients (21%) reported the absence of any of the five impairments or previous surgery. This was lower than the number among the controls, among which a majority (56%) reported no impairments or previous surgery. Hand paresthesia was the most reported impairment among both patients and controls (48% of patients and 28% of controls), followed by shoulder impairment (i.e., pain and stiffness 38% vs. 18%), and hand stiffness (34% vs. 15%). Slightly less prevalent were finger impairments, including finger locking (proxy for trigger finger) reported by 31% of the patients and 12% of the controls, and finger extension (proxy for Dupuytren's contracture and LJM) reported by 28% of the patients vs. 7% of the controls.

Eleven percent of the patients who had undergone previous CT surgery and 9% of those who had undergone previous trigger finger surgery still reported paresthesia in the operated hand. The corresponding figures for the controls were 2% and 0.1%, respectively.

Compared with the controls, patients more frequently reported bilateral impairments (53%–81% bilateral impairments in patients and 29%–69% in controls). Furthermore, patients reported coexisting impairments more frequently, i.e., 50% of patients had ≥ 2 impairments of the five investigated impairments. The corresponding figure for the controls was 21%.

Figure 4. Prevalence of upper extremity impairments in patients (black/striped) and controls (gray/white). Unilateral impairments are represented by a striped pattern (patients)/ or white color (controls) and bilateral impairments are represented by black (patients)/gray (controls).

***=P<0.001. (Reproduced with permission, *Disability and Rehabilitation*, 2019, Vol. 41, no. 6, 633–640). CT=carpal tunnel; TF=trigger finger

Activity limitations

HAQ in patients and controls

When considering the whole cohort, regardless of the presence of UEIs or not, the HAQ scores were higher (indicating greater activity limitation) in patients compared with controls (0.27 ± 0.02 vs. 0.11 ± 0.01 , $P < 0.001$). A HAQ-value ≥ 1 was seen in 10% of patients and 3% of controls. In both patients and controls, females had higher HAQ scores compared with males; female patients, 0.35 ± 0.02 vs. male patients, 0.18 ± 0.02 , ($P < 0.001$); and female controls, 0.13 ± 0.01 vs. male controls, 0.08 ± 0.01 , ($P = 0.048$).

UEIs and activity limitations

Except for flexed fingers, the presence of UEIs yielded significantly more activity limitation (a higher HAQ score) in patients than in controls (Figure 5). In the absence of UEIs, no significant differences were noted between patients and controls in activity limitation 0.05 ± 0.02 vs. 0.03 ± 0.01 , respectively ($P = 0.193$).

The highest HAQ score was observed in patients reporting hand stiffness (0.52 ± 0.03). High HAQ scores were also reported in patients who had undergone prior surgery for CT syndrome and trigger finger 0.45 ± 0.04 and 0.44 ± 0.04 , respectively, as opposed to controls who had undergone similar surgical procedures and reported lower HAQ scores of 0.09 ± 0.03 and 0.11 ± 0.11 , respectively. The coexistence of impairments increased the HAQ score, as the score for each added impairment was increased. The highest scores were observed in those patients who reported the coexistence of all five impairments. The mean HAQ score was 0.73 ± 0.07 and 40% of the patients has a HAQ score > 1 . A similar pattern was seen among the controls.

Figure 5. Health Assessment Questionnaire (HAQ)-scores in the presence of impairments or previous surgery, as well as in subjects reporting no impairment. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. CT=carpal tunnel and TF=trigger finger. (Reproduced with permission Disability and Rehabilitation, 2019, Vol. 41, no. 6, 633–640.)

Risk factors

Patients with T1D and controls

Being female, as well as a higher BMI and increasing age were common risk factors for both patients and controls, regarding several impairments. Other risk factors were only associated with impairments in either patients (with celiac disease and elevated hs-CRP) or controls (who smoked), as shown in Table 6.

When considering the patient group, females had a higher risk of all impairments, except that of flexed fingers. Two of the diabetes-related risk factors, i.e., worse metabolic control (higher HbA1c) and longer diabetes duration, were associated with an increased risk of “any UEIs” as well as shoulder impairment. Signs of macrovascular and microvascular complications (previous cardiovascular disease (CVD), kidney function, and retinopathy) showed no significant associations in the multivariate analysis, although retinopathy was associated with “any of the UEIs” in univariate logistic regression (1.86 [1.3–2.7], $P=0.001$). However, after adjustment for age, duration, BMI, smoking, celiac disease, CVD, HbA1c, GFR, and hs-CRP, retinopathy was no longer associated with the presence of UEIs. Celiac disease was associated with an increased risk of hand impairments (stiffness and paresthesia) and high hs-CRP levels were associated with finger impairments (flexed finger and finger locking).

Table 6. Multivariate regression of risk factors for UEIs in patients and controls

UEIs	Patients with diabetes		Controls	
	Risk factors	Odds ratio [CI]	Risk factors	Odds ratio [CI]
Shoulder impairment	Female sex	1.56 [1.07-2.27]	Female sex	1.91 [1.11-3.27]
	Duration	1.03 [1.01-1.06]	BMI	1.07[1.00-1.14]
	HbA1c	1.02 [1.00-1.03]	Smoking	2.97 [1.62-5.46]
Hand stiffness	Female sex	1.94 [1.31-2.87]	Female sex	2.38 [1.34-4.23]
	Age	1.03 [1.00-1.06]	Age	1.05 [1.01-1.09]
	Celiac disease	3.16 [1.10-9.02]	Smoking	2.52 [1.35-4.71]
			GFR	1.03 [1.01-1.06]
Hand paresthesia	Female sex	1.72 [1.20-2.48]	Female sex	1.91 [1.23-2.97]
	BMI	1.07[1.02-1.12]	BMI	1.08 [1.02-1.14]
	Celiac disease	5.49 [1.54-19.62]		
Finger locking	Female sex	1.49 [1.00-2.22]	Age	1.05 [1.01-1.09]
	Hs-CRP	1.18 [1.00-1.39]	CVD	2.70 [1.03-7.12]
Flexed finger	Duration	1.04 [1.01-1.07]	Age	1.06 [1.01-1.12]
	Hs-CRP	1.24 [1.05-1.47]	Smoking	4.33 [1.98-9.46]
Any UEI	Female sex	1.72 [1.01-2.27]	Female sex	2.06 [1.39-3.06]
	BMI	1.08 [1.02-1.15]	BMI	1.05 [0.99-1.11]
	HbA1c	1.03 [1.01-1.05]	Age	1.04 [1.01-1.06]
	Duration	1.05 [1.02-1.08]	Smoking	1.96 [1.13-3.39]
			GFR	1.02 [1.01-1.04]

UEI=upper extremity impairments; BMI=body mass index; Hs-CRP= high sensitivity C-reactive protein; GFR=glomerular filtration rate; CVD=cardiovascular disease. Risk factors used in the multivariate analysis for both groups included gender, age, BMI, smoking, celiac disease, CVD, GFR, and hs-CRP. In patients, the duration of diabetes, HbA1c, and retinopathy were added.

Paper II

Insulin treatment

The mean insulin dose for the whole diabetes cohort was 0.64 ± 0.29 U/kg (range: 0.13–3.56 U/kg). Patients were either treated with the MDI strategy (77% of patients) using a combination of fast-acting and long-acting insulin, or treated with the CSII strategy (23% of patients) using only fast-acting insulin in a pump. Patients undergoing MDI treatment had higher daily insulin doses than those treated with CSII (0.68 ± 0.29 U/kg vs. 0.53 ± 0.23 U/kg, respectively $P < 0.001$). The HbA1c levels showed no differences between MDI and CSII treatments (65 ± 11 mmol/mol vs. 64 ± 11 mmol/mol, respectively), $P = 0.418$.

Differences in the GH-IGF-I axis between T1D and controls

Compared with the controls, patients with T1D had lower IGF-I levels (113 ± 43 vs. 152 ± 59 , $P < 0.001$), IGF-I Z-scores (-1.31 ± 1.44 vs. 0.04 ± 1.36 , $P < 0.001$), and IGFBP-3 levels (3.13 ± 0.69 vs. 3.78 ± 0.8 , $P < 0.001$), but higher levels of IGFBP-1 (median; 68 [37–160] vs. 21 [11–34], $P < 0.001$) and GH (0.74 [0.25–2.46] vs. 0.57 [0.15–2.08]), $P = 0.025$, respectively.

IGF-I in diabetes

IGF-I Z-scores and subcutaneous insulin (exogenous)

A positive correlation was observed between the IGF-I Z-scores and the insulin dose, $r = 0.160$, $P < 0.001$. When we categorized insulin doses and investigated their impact on the IGF-I Z-scores, a positive relationship was noted with the IGF-I Z-score $r = 0.178$, $P < 0.001$. However, even in the highest insulin category (> 1.0 U/kg), the IGF-I Z-scores were still subnormal, in comparison with those of the non-diabetic controls (Figure 6).

Figure 6. Insulin-like growth factor-I (IGF-I) Z-score (mean 95% CI) in relation to increasing insulin doses (U/kg). ** $P < 0.01$; *** $P < 0.001$ compared with controls. The number of subjects (n) in each category was <0.41 , $n = 68$; $0.41-0.6$, $n = 229$; $0.61-0.8$, $n = 162$; $0.81-1.0$, $n = 62$; and >1.0 , $n = 28$; control, $n = 549$. (Reproduced with permission Clinical Endocrinology, 2018, Volume 89, Issue 4, p 424–430)

IGF-I Z-score and endogenous insulin secretion (C-peptide)

Residual endogenous insulin secretion, assessed by the levels of fasting C-peptide, was detectable in 65 of 526 patients, and was further categorized into three groups: 1) not detectable; 2) 1–99 pmol/L and 3) >100 pmol/L. Even at very low C-peptide levels, the IGF-I Z-score was higher (-0.5 ± 1.2) than when no C-peptide was detectable (-1.4 ± 1.4), $P=0.001$. In patients with the highest detectable C-peptide levels (>100), the IGF-I Z-scores showed no significant difference from those of the controls (Figure 7).

Figure 7. Insulin-like growth factor-I (IGF-I) Z-score (mean 95% CI) in relation to endogenous insulin secretion, assessed by fasting C-peptide levels. * $P<0.05$; *** $P<0.001$ compared with controls. The number of subjects (n) in each category was 0, $n=461$; 1–99, $n=47$; 100+, $n=18$; control, $n=549$. (Reproduced with permission Clinical Endocrinology, 2018, Volume 89, Issue 4, p 424–430.)

IGF-I and UEIs

No association was found between the IGF-I Z-score and our five predefined UEIs (shoulder pain and stiffness, hand paresthesia, hand stiffness, finger locking, and finger extend) in patients with diabetes.

Metabolic factors and the IGF system in patients and controls

The relationship between metabolic factors (BMI and fasting glucose) and the IGF system was further analyzed. As shown in Figure 8, BMI and fasting glucose were positively correlated in both patients and controls, possibly indicating insulin resistance. The logGH was negatively correlated with fasting glucose in both groups, as it was with the IGF-I Z-score in patients. Regarding the logIGFBP-1, opposite results were found in the controls and patients. The controls showed a negative correlation between the logIGFBP1 and fasting glucose ($r=-0.304$), whereas patients showed a positive correlation ($r=0.413$).

Figure 8. Correlations between the IGF system, BMI, and fasting glucose, using Pearson's correlation. * $P<0.05$, ** $P<0.01$, and *** $P<0.001$. IGF=insulin-like growth factor; BMI=body mass index; IGFBP=insulin-like growth factor-binding protein; GH=growth hormone.

We looked further into these phenomena by categorizing fasting glucose into: 1) normal <5 and $5.1\text{--}6.0$ mmol/L; 2), impaired fasting glucose (IFG) $6.1\text{--}6.9$ mmol/L; and 3) diabetic $7.0\text{--}9.9$, $10.0\text{--}14.9$, and >15 mmol/L. As shown in Figure 9, the log IGFBP-1 was reduced with increasing plasma glucose concentrations in the controls. In patients however, the log IGFBP-1 was increased with higher levels of fasting glucose >7 mmol/L, but showed no change in the non-diabetic range.

Figure 9. LogIGFBP-1 in relation to fasting plasma glucose categorized as normal <5.0 and $5.1\text{--}6.0$ mmol/L; impaired fasting glucose (IFG), $6.1\text{--}6.9$ mmol/L; diabetic, $7.0\text{--}9.9$, $10.0\text{--}14.9$, and >15.0 mmol/L among controls (filled squares) and patients (filled circles). Values represent the mean (95% CI). * $P<0.05$; *** $P<0.001$ compared with fasting plasma glucose <5.0 mmol/L. The number of subjects (n) in each category was as follows: controls <5 mmol/L, $n=88$; $5.1\text{--}6.0$ mmol/L, $n=338$; $6.1\text{--}6.9$, $n=82$; and in patients <5.1 mmol/L, $n=57$; $5.1\text{--}6.0$ mmol/L, $n=47$; $6.1\text{--}6.9$ mmol/L, $n=49$; $7.0\text{--}9.9$ mmol/L, $n=151$; $10.0\text{--}14.9$ mmol/L, $n=195$; ≥ 15 mmol/L, $n=89$. (Reproduced with permission Clinical Endocrinology, 2018, Volume 89, Issue 4, p 424–430).

Paper III

HRQOL in patients and controls

General differences in HRQOL

The overall perceived HRQOL was lower in patients compared with the controls (Table 7). The most marked difference between patients and controls was observed in general health (59 ± 26 vs. 74 ± 22 , $P<0.001$). The smallest difference was observed in mental health (77 ± 18 vs. 81 ± 16 , $P<0.001$). The presences of T1D reduced both the role-physical and bodily pain scores by 10 points each, compared with the controls.

Females patients and controls had lower scores than males, and the greatest difference in female patients was observed in bodily pain (female patients 59 ± 26 vs. male patients 69 ± 27 patients, $P<0.001$). The greatest difference between female and male controls was observed in the role-emotional scores (84 ± 34 and 94 ± 21 , respectively, $P<0.001$).

Table 7. Comparison of HRQOL (SF-36) scores between patients and controls of both sexes

SF-36 subscales	Patients (All)	Controls (All)	Patients		Controls	
			Female	Male	Female	Male
Physical function	80 ± 23	$87\pm 19^*$	$76\pm 24^{a,c}$	$85\pm 20^{b,c}$	$85\pm 20^{a,d}$	$90\pm 16^{b,d}$
Role physical	72 ± 38	$82\pm 34^*$	$68\pm 39^{a,c}$	$77\pm 36^{b,c}$	$79\pm 36^{a,d}$	$86\pm 30^{b,d}$
Bodily pain	64 ± 27	$74\pm 25^*$	$59\pm 26^{a,c}$	$69\pm 27^{b,c}$	$71\pm 26^{a,d}$	$78\pm 24^{b,d}$
General health	59 ± 26	$74\pm 22^*$	$57\pm 26^{a,c}$	$62\pm 25^{b,c}$	$73\pm 23^{a,d}$	$77\pm 20^{b,d}$
Vitality	55 ± 26	$67\pm 24^*$	$51\pm 26^{a,c}$	$60\pm 25^{b,c}$	$63\pm 25^{a,d}$	$72\pm 21^{b,d}$
Social functioning	82 ± 23	$89\pm 20^*$	$80\pm 24^{a,c}$	$85\pm 22^{b,c}$	$86\pm 22^{a,d}$	$92\pm 16^{b,d}$
Role emotional	81 ± 33	$88\pm 30^*$	79 ± 35^c	$84\pm 31^{b,c}$	84 ± 34^d	$94\pm 21^{b,d}$
Mental health	77 ± 18	$81\pm 18^*$	$75\pm 18^{a,c}$	$80\pm 18^{b,c}$	$79\pm 18^{a,d}$	$84\pm 16^{b,d}$

$P<0.05$ for analysis of patients with diabetes vs. controls. Letters a–d indicate significance ($P<0.05$) when analyzed separately for gender. a=female with type 1 diabetes vs. control female; b=male with type 1 diabetes vs. control male; c=female with type 1 diabetes vs. male with type 1 diabetes; d=control female vs. control male.

Upper extremity impairments in type 1 diabetes and HRQOL

Patients who reported the presence of UEIs had a significantly lower perceived HRQOL compared with asymptomatic patients (Figure 10). Patients who reported no UEIs had equivalent HRQOL-scores with the controls. When multiple coexisting impairments were present, the patients had a lower perceived HRQOL.

Figure 10. Short Form 36 (SF-36) scores in patients with diabetes in relation to the number of upper extremity impairments (shoulder pain and stiffness, hand paresthesia, hand stiffness, finger locking, or flexed finger). (Reproduced with permission Disability and Rehabilitation, 2020; DOI: 10.1080/09638288.2019.1705924)

In an attempt to investigate plausible explanatory factors for the perceived HRQOL, we performed multiple linear regression considering the eight SF-36 dimensions as dependent variables, and age, gender, diabetes duration, HbA1c, retinopathy, and the presence of UEIs as independent variables.

As shown in Table 8, the presence of shoulder impairment, hand paresthesia, and hand stiffness were all independently associated with a lower HRQOL in all dimensions, with two exceptions: mental health (shoulder impairment) and role-emotional (hand paresthesia). Finger impairments (finger locking and flexed finger) did not seem to independently affect the perceived HRQOL in patients, in contrast to the controls in whom finger locking and flexed fingers were associated with a lower HRQOL (i.e., in bodily pain, general health, vitality, and physical function).

Table 8. SF36 dimensions significantly related to UEIs in patients

UEIs	Patients*
Shoulder pain and stiffness	PF, RP, BP, GH, V, SF, RE
Hand paresthesia	PF, RP, BP, GH, V, SF, MH
Hand stiffness	PF, RP, BP, GH, V, SF, RE, MH
Finger locking	
Flexed finger	

*Multiple linear regression where respective SF-36 dimensions were set as dependent variables, and the independent variables were UEIs, age, gender, HbA1c, diabetes duration, and retinopathy. UEIs=upper extremity impairments; PF=physical function; RP=role-physical; BP=bodily pain; GH=general health; V=vitality; SF=social functioning; RE=role-emotional; and MH=mental health.

Other risk factors associated with the HRQOL in patients

Gender, age, and HbA1c

In our multiple regression model, a higher HbA1c level was independently associated with a lower HRQOL in all SF-36 dimensions, except for role-emotional and mental health. Female patients showed lower physical function and lower bodily pain, and a higher age was associated with lower scores of physical function, bodily pain, and vitality.

Sick leave in patients and controls

Self-reported sick leave or disability pension was cited by 23% of the patients and 11% of the controls. Among these, about every second participant cited musculoskeletal impairments as one reason (in total, 11% of all patients and 5% of the controls).

PAPER IV

Reliability analysis of the questionnaire

The mean time between the test-retest was 13 ± 8 days. Test-retest analysis of all items in the questionnaire showed an agreement ranging from 80.3%–98.4% for self-reported shoulder, hand, and finger impairments.

Self-reported upper extremity impairments

Shoulder stiffness was reported by 49% of the patients as being the most common impairment (Table 9). Shoulder pain was reported by 44% of the patients and hand pares-thesis by 40%.

A significant association was observed between self-reported impairments, i.e., shoulder stiffness was associated with shoulder pain ($r=0.612$), $P<0.001$. Shoulder stiffness was also associated with hand and finger impairments, specifically hand stiffness ($r=0.254$, $P=0.039$); reduced hand strength ($r=0.327$); previous CT surgery ($r=0.315$); finger locking ($r=0.317$); and hand nodules ($r=0.361$), all $P<0.001$. When we analyzed the self-reported impairments from the LedIG cohort (study I), we observed similar correlations.

Table 9. Prevalence of the self-reported upper extremity impairments.

Self-reported UEIs	Prevalence % (bilateral*%)
Shoulder pain	44 (64)
Shoulder stiffness	49 (78)
Shoulder pain and stiffness	35 (66)
Hand pain	35 (77)
Hand stiffness	24 (75)
Hand tingling-numbness	40 (70)
Awakening to tingling fingers	26 (73)
Hand paresthesia [#]	45 (71)
Reduced hand strength	29 (72)
Previous CT surgery	14 (64)
Finger locked	22 (45)
Hand nodules	15 (47)
Previous TF surgery	9 (67)
Finger extension	9 (78)

*Percentage of patients with respective upper extremity impairments (UEIs) with bilateral impairments. #Hand paresthesia=tingling fingers and/or awakening to tingling fingers. CT=carpal tunnel and TF=trigger finger.

Clinical examination of upper extremity impairments

Of the 69 patients who participated in this study, 65% had at least one clinical UEI. The most common detected impairment was the inability to place the “hands behind the back,” which was observed in 40% of the patients (Figure 11). The second most prevalent findings were signs of CT syndrome, as tested by the Tinel’s and Phalen’s tests, and observed in 27% of the patients. Previous surgery for trigger finger and CT syndrome was reported in 13% of the patients and a positive prayer’s sign was detected in 24%. Clinical findings varied regarding the predominance of unilateral or bilateral test results. Trigger fingers and painful nodules were only found unilaterally in the cohort subjected to clinical investigation, whereas the inability to place the hands against the back and clinical findings of fibrotic string structures were found bilaterally in 70%–75% of patients with impairments.

Figure 11. Prevalence of clinically examined unilateral and bilateral upper extremity impairments. Reproduced with permission of Journal of Diabetes Research, 2020; DOI: 10.1155/2020/4172635.)

Clinically evaluated shoulder impairments were associated with each other, i.e., “hands to back” was correlated with “hands to roof”, $r=0.553$, $P<0.01$, and with “hands behind head” $r=0.881$, $P<0.01$. Shoulder impairments were also associated with hand and finger impairments e.g., “hands to back” was associated with a positive prayer’s sign $r=0.485$, $P<0.01$.

Shoulder mobility and grip force

Shoulder mobility were similar in men and women, except for abduction, for which females had lower mobility ($146^{\circ}\pm 41^{\circ}$ vs $163^{\circ}\pm 26^{\circ}$, $P=0.038$). Grip force was measured in all patients, and females were weaker than males 165 ± 76 N vs. 300 ± 12 N, $P<0.001$.

Self-reported versus clinical examination of upper extremity impairments

We found significant relationships between self-reported UEIs and clinical evaluated impairments. Those patients who reported shoulder stiffness also had reduced shoulder mobility (as determined by goniometer testing) in all five axes tested, compared with those reported no shoulder stiffness (Table 10). In both female and male patients, grip force was lower in those who reported impaired grip force (females 124 ± 51 N vs. 190 ± 79 N, $P=0.014$, and males 181 ± 92 N vs. 336 ± 108 N, $P=0.001$).

Table 10. Test between self-reported versus clinical examination of shoulder stiffness and reduced hand strength

	All participants	Patient self-reporting		P-value
		<i>Shoulder stiffness</i>	<i>No shoulder stiffness</i>	
Shoulder mobility (Goniometer)[¤]	(n=69)	(n=33)	(n=35)	
Flexion shoulder (°)	162±16	153±17	170±8	< 0.001
Extension shoulder (°)	60±9	56±10	63±6	0.001
Abduction shoulder (°)	154±35	136±32	171±32	< 0.001
Inward rotation shoulder (°)	43±17	36±15	51±16	< 0.001
Outward rotation shoulder (°)	64±25	53±24	76±20	< 0.001
		<i>Reduced hand strength</i>	<i>No reduction in hand strength</i>	
Grip force (Grippit)[^]	(n=69)	(n=20)	(n=48)	
All (N)	231±122	147±74	269±120	< 0.001
Male (N) [#]	300±123	181±92	336±108	0.001
Female (N) [#]	165±76	124±51	190±79	0.014

Data are presented as mean±SD. P-values analyzed between patients with and without shoulder stiffness and those with and without reduced hand strength. [¤]The lowest obtained value in degrees from the five goniometer measurements. [^]The lowest obtained Gripping value (in Newtons) for either left hand or right hand. [#]Male participants, n=34 (eight reported reduced hand strength and 26 reported no reduction in hand strength); female participants, n=35 (12 reported reduced hand strength, 22 reported no reduction in hand strength).

Self-reported shoulder stiffness was related to our three clinical shoulder movement tests, i.e., “hands behind head” $r=0.429$, $P<0.01$, “hands against back” $r=0.546$, $P<0.01$, and “hands to roof” $r=0.501$, $P<0.01$ (Table 11).

In addition, patients who self-reported the presence of finger impairments more often had clinical impairments, e.g., positive correlations were found between self-reported previous trigger finger surgery and a positive prayer’s sign $r=0.456$, $P<0.01$; reduced thenar strength $r=0.252$, $P<0.252$; trigger finger $r=0.308$, $P<0.01$; and painful hand nodules $r=0.507$, $P<0.01$.

Table 11. Clinical UEIs significant correlated to self-reported UEIs

CLINICAL EXAMINATION		
Shoulder pain	HBH / HAB / HTR / Flex / Ext / ABd / InwRot / OutRot / Grip	
Shoulder stiffness	HBH / HAB / HTR / Flex / Ext / ABd / InwRot / OutRot / Phalens / Prayer	
QUESTIONNAIRE	Hand Pain	Grip / Prayer / TF
	Hand stiffness	Flex / Grip / Tinel / Thenar / TF
	Tingling fingers	
	Wake up to tingling fingers	
	Reduced hand strength	HAB / HTR / Flex / OutRot Grip / Prayer / TF / Thenar / Fibrosis
	Finger locked	OutRot / Tinel / Prayer / TF / Fibrosis
	Hand nodules	InwRot
	Flexed finger	Grip / Prayer / TF / Thenar / Nodules
	Previous CT surgery	HAB / HTR / OutRot / Prayer
	Previous TF surgery	HBH / HAB / Ext / InwRot / OutRot / Prayer / Thenar / TF / Nodules

HBH=Hands behind head; HAB=Hands behind back; HTH=Hand to roof; Flex=shoulder flexion, Ext=shoulder extension, Abd=shoulder abduction, InwRot=shoulder inward rotation; Out-Rot=shoulder outward rotation; TF=trigger finger; Grip=grip force; Fibrosis=fibrotic string

DISCUSSION

Paper I and IV

Prevalence of self-reported UEIs

The LedIG study is, to our knowledge, the first large-scale, population-based study to present the prevalence of UEIs in patients with a long duration of T1D and compare those findings with those of controls without diabetes. The prevalence of various self-reported UEIs in patients with T1D was 28%–48%, which was 2–4 times more prevalent than in the controls (Paper I). In paper IV, one aim was to relate self-reported UEIs to clinical findings, and possibly facilitate the development of key questions for use in clinical practice to identify individuals at risk. The cohort was considerably smaller than that of the LedIG cohort (69 vs. 773, respectively) and included patients with a shorter disease duration. In papers I and IV, the prevalence of UEIs was high, i.e., 79% and 65%, respectively. Self-reported lifetime prevalence of any upper limb soft tissue lesion was 72% in another T1D outpatient population⁷⁸. In the DCCT-EDIC cohort, which had a similar duration to our LedIG cohort, but was not population based, Larkin et al.⁴⁴ investigated 1217 patients with T1D. They employed both self-reported questionnaires and clinical investigation and found that 66% of the patients with long-standing T1D reported the presence of UEIs⁴⁴.

As the LedIG study aimed to cover a large population of patients with long-standing T1D, we invited all patients fulfilling these criteria residing in the south-eastern region of Sweden (catchment area of nine hospitals). Furthermore, the study was designed using a case-control approach and included matched controls without diabetes. The study was questionnaire-based, using both previously well-known and validated instruments (the SF36 and HAQ), as well as questions developed by our research group to cover UEIs and background data. In the analysis of the LedIG data, we constructed UEI proxy variables to include diabetes-related problems i.e., 1) adhesive capsulitis (shoulder pain and stiffness/shoulder impairment); 2) LJM (hand stiffness); 3) CT syndrome (hand paresthesia); 4) trigger finger (finger locking); and 5) Dupuytren's contracture (flexed finger).

Making a direct comparison of our results with those of previous studies was somewhat difficult, owing to variations in study design, including the type of diabetes, diabetes duration, sample size, diagnostic criteria, and methodology used. Several previous smaller, non-population-based studies, which included both T1D and T2D, have shown an increased prevalence of UEIs among patients with diabetes compared with controls^{48,67,88}.

It is unclear whether impairments differ between type 1 and 2 or are similar in both types of diabetes. A meta-study by Zreik et al.⁸⁹ showed no differences regarding adhesive capsulitis between T1D and T2D. In contrast, Arkkila et al.⁹⁰ investigated shoulder impairment in a mixed cohort and found a higher frequency in the T2D cohort than in the T1D cohort (22% vs. 10%). However, the mean age of the two groups showed considerable differences (33 vs. 61 years). The large-scale study of Larkin et al.⁴⁴ was part of the DCCT/EDIC study, which exclusively investigated patients with T1D. This cohort was very similar to our LedIG cohort, both in terms of the long duration (31 years vs. 35 years) and age (52 years vs. 50 years). This DCCT/EDIC cohort however, did not include a control group without diabetes.

Shoulder pain in the general population shows a prevalence that varies between 7%–27% and adhesive capsulitis represents approximately 2%–5% of that figure^{89,91}. In our LedIG population, 38% of the patients with T1D reported shoulder impairment, i.e., pain and stiffness. These symptoms are suggestive of, but not exclusive to, adhesive capsulitis and were found to be twice as frequent in patients than in controls (18%). In patients with T1D in Sardinia, adhesive capsulitis was diagnosed in 35.1%. In another study of T1D with a long duration (>45 years), 59% of the patients had frozen shoulder⁹². The prevalence of adhesive capsulitis in the large T1D cohort described in Larkin et al. was 31%. Thus, taken together, around one third of the patients with long-standing diabetes seem to have shoulder impairments.

Self-reported LJM (hand stiffness), CT syndrome (hand paresthesia), trigger finger (finger locking), and Dupuytren's contracture (flexed finger) were also common (Papers I and II) in agreement with other studies in patients with T1D^{44,78,93}. Similar to the findings of Larkin et al.⁴⁴, previous surgery for CT and trigger finger were common in patients with T1D. The present study reported that about every fourth patient (22%–26%) had previous surgery for CT or trigger finger, which is considerably higher than the value reported for non-diabetic controls, of whom 1%–5% reported previous surgery for such conditions. Interestingly, we found that 25% of the patients reporting previous CT surgery and 22% of those with previous surgery for trigger finger still had symptoms, which may reflect more vulnerable tissues in diabetes⁹⁴. Another plausible explanation for this finding is that the remaining symptoms represented signs of diabetic neuropathy. Whether the outcomes of shoulder and hand surgery differ between patients with and without diabetes is not entirely clear^{95–97}. A recent retrospective study concluded that patients with diabetes experience more symptoms before and after CT surgery, but can expect the same relative improvement from surgery as patients without diabetes⁹⁸.

Prevalence of UEIs by clinical examination

We aimed to determine the prevalence of UEIs in patients with T1D by clinical examination in a smaller cohort of patients with T1D, in conjunction with routine clinical

visits (as a complement to the self-administered questionnaire). We also aimed to develop simple investigation methods that can be performed in a clinical setting.

Of the three clinical shoulder tests (goniometer tests not included), “hands behind back” was the most common test that patients failed to perform. Four out of ten patients were unable to perform this test, followed by the “hands to roof” test (which 20% of the patients were unable to perform). The diagnostic criteria for frozen shoulder differs; however, the common denominators of frozen shoulder are pain, stiffness, and symptoms of impaired mobility^{44,63,93}. Although a variety of shoulder examination techniques have been suggested for diagnostic testing, none shows perfect specificity or sensitivity^{99–102}. In our studies, we could not make direct correlations with diagnoses of frozen shoulder. However, our results obtained by self-reporting and clinical examination of the shoulder highlight that shoulder impairment is a common finding in T1D, affecting around four out of every 10 patients.

The positive Phalen’s test (27%) and Tinel’s test (26%) were suggestive of CT syndrome, and were also consistent with the findings of Larkin et al. (30%)⁴⁴. Twenty-four percent of our patients had a positive prayer’s sign, which is considered diagnostic for LJM [103], compared to 22% reported by Larkin et al.⁴⁴. Like the self-reported UEIs, clinical finger impairments were the least prevalent of the investigated impairments.

Similar to the self-reported impairments, we found that clinical impairments were related to each other, e.g., patients with a positive prayer’s sign more often had shoulder impairments and TF, as well as a reduced grip force. These findings suggest that patients with T1D might have more general alterations in soft tissues⁹³.

Self-reported UEIs versus clinical impairments and possible key questions

The implementation of a strategy to capture UEIs on a regular basis in diabetes clinics is warranted. However, to our knowledge, there is no established procedure to record and evaluate upper UEIs in patients with T1D at regular check-up visits. In paper IV, we compared self-reported UEIs with a clinical examination of patients with T1D.

Interestingly, we found that self-reported shoulder pain and stiffness were significantly associated with clinically detected impaired shoulder mobility. Self-reported shoulder stiffness was also associated with a higher risk of a positive prayer’s sign and a positive Phalen’s test. Thus, asking patients about shoulder pain and stiffness could be useful in identifying the patients at risk and in need of further investigation.

In addition, patients who reported reduced hand strength also had an objectively lower grip force than those who did not. Furthermore, these patients with self-reported reduced hand strength had a higher risk of clinical shoulder impairments, a positive

prayer's sign, TF, and palmar fibrotic strings. Thus, asking patients whether they have reduced hand strength might also be valuable in identifying individuals in need of further evaluation.

Another important finding in paper IV was that of self-reported surgery for TF and CT syndrome, which showed a significant association with the presence of clinical UEIs, including an increased risk of shoulder impairment, and a positive prayer's sign, TF, and nodules (the latter two only regarding previous TF). These findings indicate that impairments may often coexist and patients with previous CT or TF surgery could be regarded as a risk group for UEIs.

Reliability of a self-administered questionnaire

Our test-retest analysis showed favorable reproducibility. No precise time-difference was established in measuring the questionnaire reliability; however, this should be long enough to prevent memorization of the previous answers, but short enough to prevent any considerable change in symptoms over time¹⁰³. We reasoned that a period of 2 weeks would be an optimal range to minimize memory recollection and prevent the risk of actual change in symptoms, which may affect the results. The average time between the test-retest in study IV was 13.8 days. Identical answers on both occasions were observed in 80%–98% of the responses. The highest agreement was observed in the questions on previous surgery (97%–98%) and finger extension/finger locking (91%–98%). Lower figures were observed in more subjective, and perhaps intermittent symptoms, e.g., tingling (80%–85%).

UEIs and activity limitation

As UEIs are common in T1D, another important research question was to determine whether UEIs are related to activity limitation (disability) in T1D compared with controls. Thus, we used the well validated HAQ-DI. Interpretation of the HAQ score varies between authors, who claim a minimal difference between 0.1–0.22 to be clinically important⁸⁰. Overall, patients showed greater activity limitation compared with the controls (0.27 vs. 0.11). A Finnish study estimated normative values for HAQ-DI in the general population and reported a mean of 0.25¹⁰⁴. Compared with the Finnish study, our patients showed no significant deviation from the controls. In a smaller study by Ramchurn et al.⁸⁸ (comprising a mixed cohort of T1D and T2D patients), patients with T1D had a mean HAQ score of 0.22, which is in line with our findings.

Females had higher HAQ scores compared with males, both in patients (0.35 vs. 0.18) and controls (0.13 vs. 0.08). Corresponding figures from the Finnish study on the general population reported a HAQ score of 0.28 in females and 0.18 in males¹⁰⁴.

An individual's experience of disability is the result of multiple factors, e.g., nature and severity of the disease, individual personal attributes, and environmental circumstances⁵⁸. Thus, such results can be difficult to compare between different populations.

In the present study, patients with T1D and UEIs reported higher HAQ scores (indicating more activity limitation) than those who did not report the presence of UEIs, which supports previous findings^{44,67,105}. Furthermore, the HAQ scores were higher with each additional impairment. In absence of any impairment, HAQ scores in patients were consistent with those of the controls who reported no UEIs. Ramchurn et al.⁸⁸ found a similar increase in HAQ scores with multiple UEIs. Larkin et al.⁴⁴ who used the Disabilities of the arm, shoulder, and hand (DASH) questionnaire found increased activity limitation with the presence of several coexisting UEIs.

In rheumatology, a HAQ score ≥ 1 , which represents extensive disability, is used as an indicator in clinical practice for further problem-solving regarding possible needs for multi-professional interventions¹⁰⁶. In a well-defined early rheumatoid arthritis cohort, a HAQ score ≥ 1 was found in 36% of the patients 8 years after diagnosis¹⁰⁶. In our T1D group, 10% had an HAQ score ≥ 1 , and in the subgroup with hand stiffness, 21% had an HAQ score ≥ 1 .

UEIs and risk factors

Female patients had an increased frequency of shoulder and hand impairments among both patients and controls (Paper I), which is in agreement with previous reports^{44,48}. Another similarity in both groups was that a higher age and BMI were associated with hand stiffness and hand paresthesia. The BMI is a known risk factor for CT syndrome, both in patients with diabetes⁸¹ and in non-diabetic individuals¹⁰⁷. The mechanism behind the increased risk is not fully understood but may be, in part, due to a higher intra-carpal pressure (because of an excess of adipose tissue) within the CT, which inhibits blood flow and increases the risk of nerve ischemia. The underlying mechanisms may also involve peripheral neuropathy¹⁰⁸.

We also found differences in the risk profile between patients and controls. For example, smoking was a significant risk factor for shoulder, hand, and finger impairments in controls but not in patients. We measured hs-CRP, as a marker of inflammation, and found that shoulder and hand impairments were not associated with inflammation, which is consistent with the findings of Bridgman et al.⁵¹. However, a significant relationship was noted between hs-CRP and finger impairments, implying that low-grade inflammation may be associated with UEIs (finger) in T1D. This is a novel finding, which to our knowledge, had not been reported previously.

We found significant relationships between glycemic control and shoulder impairment as well as any of the UEIs (Paper I). Glycemic control, as measured by HbA1c, has previously been associated with shoulder and hand impairments in T1D^{44,88}. However, reports have been inconsistent^{45,59,109,110}. In a large retrospective study, including both T1D and T2D, Yian et al.¹¹¹ found no correlation between frozen shoulder and HbA1c, and those authors speculated that a certain specific glycemic threshold might be necessary for the condition to develop.

The UEIs have been also associated with microangiopathy and neuropathy⁴⁴. In the present study, laser-treated retinopathy, a manifestation of microangiopathy, was associated with an increased risk of any UEI in univariate but not in multivariate analysis. These findings suggest that the relationship might be indirect and may be due to other variables. Previous studies have reported a higher incidence of retinopathy in patients with T1D and UEIs, as compared with those without such conditions, even after adjustment for diabetes duration^{112,113}. A new observation in the present study was that celiac disease seems to be a risk factor for hand paresthesia in patients. Both CT syndrome and celiac disease have previously been reported to be associated with neuropathy^{114,115}. Overall, our study suggests several risk factor profiles for the investigated impairments, which supports previous theories of heterogeneous etiologies⁴⁵.

Paper II

Differences in the IGF system between patients with T1D and controls

In the present study, IGF-I and IGFBP-3 levels were lower in patients and IGFBP-1 and GH-levels were higher compared with the controls. These findings support those of previous reports, which have shown that the IGF system is altered in T1D^{116,117}. Our controls had a mean IGF-I Z-score of 0.04 ± 1.36 , i.e., close to zero, indicating a representative control group.

An interesting difference was observed between patients and controls regarding the association between fasting glucose and IGFBP-1 levels. A negative correlation was seen in controls, i.e., lower IGFBP-1 with increasing fasting glucose, but a positive correlation was observed in patients. In the general population, IGFBP-1 levels are thought to reflect hepatic insulin sensitivity²⁴. A possible explanation for the inverse correlation between fasting blood glucose and IGFBP-1 in the controls might be increasing insulin resistance accompanied by higher glucose levels in the non-diabetic range. This reasoning is supported by our findings of higher fasting glucose with higher BMI in the controls. Ketoacidosis, defined by an acute insulin deficiency is associated with a direct increase in IGFBP-1 levels, which can be reversed with insulin administration¹¹⁸. Hence, the positive correlation between IGFBP-1 and glucose observed in patients with T1D might be indicative of insulin deficiency and might be clinically useful. Glucose is not a regulator of IGFBP-1¹¹⁹.

Associations between residual endogenous insulin secretion (C-peptide) and the IGF system

Similar to Wang et al.⁷, we found that 12% of the patients still had endogenous insulin secretion (C-peptide). In a smaller study, Hedman et al.³² reported higher circulating IGF-I levels in T1D, with C-peptide levels >100 pmol/L than with C-peptide <100 pmol/L. The present study confirms this observation and demonstrates that even very low C-peptide (1–99 pmol/L) levels are associated with higher IGF-I levels. One explanation for this finding is that the dysregulated IGF system is induced by intraportal

insulin deficiency, and treatment with intraperitoneal insulin, which is absorbed into the portal vein increases circulating IGF-I levels^{117,120}. In the present study, the total insulin dose (U/kg) correlated positively with IGF-I levels, indicating that subcutaneous insulin administration affects IGF-I levels in T1D, which is in agreement with the findings of previous reports^{120,121}. When we categorized the insulin dose in 0.2 U/kg intervals, IGF-I was increased with an increasing insulin dose. However, even with the highest dose of insulin (> 1.0 U/kg), the IGF-I Z-score was still lower in patients compared with the controls, indicating that exogenous subcutaneous insulin cannot fully restore the IGF system in T1D.

Possible associations between UEIs and the IGF system

Krause et al.¹²² described hormonal alterations in diabetes and the detrimental effects of T1D on skeletal muscle. We also know that IGF-I is important for skeletal and muscular growth¹²³. We therefore hypothesized that low circulating IGF-I could be a contributor to the common UEIs observed in diabetes. However, no such relationship was found in our LedIG cohort. Thus, centrally secreted IGF-I does not seem to be a risk factor for UEI. This does not exclude the notion however, that a more local imbalance, i.e., para/autocrine IGF-I expression at the tissue level, might be of importance¹²⁴, however this was not investigated.

Paper III

HRQOL in patients with T1D vs. controls

The present study is as far as we know, the first population-based study to demonstrate that the HRQOL in patients with T1D experiencing UEIs is lower compared with that of controls. The SF-36 has been used to measure the health status of many different populations. As a generic measure, it facilitates comparisons between different diseases. The SF-36 especially provides a measure of functional health status. Available reference values, as opposed to disease-specific measurements, makes comparisons possible⁸³. Our scores from the control group were in line with those reported earlier in Swedish reference data⁸³.

In the present study, the overall perceived HRQOL in patients was lower (for all eight SF-36 dimensions) compared with that in the controls. The most remarkable difference was observed in the dimension of general health (-15 points). General health is strongly associated with physical health status, and this finding indicates that T1D has a negative effect on physical function. A Danish study by Nielsen et al.¹²⁵ reported a five-point reduction for the corresponding dimension using SF-12, which is a shorter version of the SF-36 (12 questions vs. 36)¹²⁶.

Diabetes has been associated with depression^{127,128}. In the present study, mental health was negatively affected by T1D (-4 points), but not to the extent to which the physical

dimensions were affected. There are few studies for comparison. Nielsen et al.¹²⁵ found small but significant differences for the corresponding dimension.

Gender differences

In the present study, females with T1D reported lower HRQOL scores than males in both groups. Numerous studies have reported a lower health status in diabetic women compared with men^{71,129}, which is consistent with the findings of studies in the general population¹³⁰.

In the present study, the greatest difference between male and female patients was observed in bodily pain. It has been proposed that female subjects may be more vulnerable to pain¹³¹. The greatest difference between female and male controls were observed in the dimension of role-emotional; as female controls reported lower scores than male controls.

HRQOL in patients with T1D and controls with UEIs

We have shown that UEIs are extremely common in the diabetes population. Thus, we found it important to address the possible impact of UEIs on perceived HRQOL. As far as we know, only one previous study has addressed health status in relation to UEIs exclusively in patients with T1D⁷⁸.

Similar to that study, we found that shoulder and hand impairments, but not finger impairments were negatively affected by the perceived HRQOL. In those patients who reported no UEIs, we found health status to be similar to that of the controls, indicating that the presence of UEIs may considerably affect the perceived HRQOL.

Glycemic control (HbA1c) seemed to affect the perceived HRQOL (in all dimensions, except role-emotional and mental health); however, the impact was rather small, which is consistent with the findings of a recent study¹³². Several earlier studies have not been able to determine a relationship between HbA1c levels and HRQOL^{133,134}.

Impaired physical function in diabetes has been reported previously^{81,105}. Redmond et al.⁸¹ investigated disability in a mixed cohort of T1D and T2D patients with hand syndromes, and found marked activity limitations in all dimensions of the SF-36. As reported by Redmond et al., we found significant gender differences, which could in part, be due to physical differences between the sexes, e.g., lower grip force in females compared with males.

Sick leave in patients with T1D and controls

We further investigated the effects of UEIs on work ability and found that 23% of the patients and 9% of the controls reported work incapacity. We have not found many other previous reports for comparison. Nielsen et al.¹²⁵ demonstrated that patients with T1D had 12% more sick leave per year compared with the general population. In that study, no explanations for those findings were discussed. In the present study, approximately half of the patients on sick leave reported musculoskeletal complications (back, muscle, or joint problems) as one of the reasons for sick leave. Thus, musculoskeletal

impairments seem to play a significant role in work incapacity associated with long-standing T1D. It is important to gain a deeper understanding of work incapacity in diabetes to facilitate the establishment of appropriate interventions.

Limitations

This thesis includes studies with a cross-sectional design, and therefore no causal associations can be made. In both study cohorts, response rates were moderate, which could raise questions concerning the validity of the collected data. Individuals with symptoms might have been more motivated to participate (selection bias). Attempts were made to increase the response rate by sending reminders and contacting patients by phone (laboratory dropouts).

Except for paper IV, UEIs were assessed using a self-reported questionnaire, and thus cannot be diagnostic. However, our results on UEI prevalence were consistent with those of another large cross-sectional study of patients with T1D, of a similar age and with a similar diabetes duration⁴⁴, which could strengthen our data. Another aspect of self-reported data that needs to be considered is the risk of recollection errors, e.g., regarding insulin dosage, body weight, and other clinical characteristics. However, in paper IV, we addressed the reliability issues and could show that the questionnaire constructed by our group showed reliability over time.

Background data like education and socioeconomic status are examples of factors that could affect the HRQOL and HAQ scores, and would preferentially have been included in the study. Furthermore, another limitation in the study of metabolic control as a possible risk factor was the cross-sectional design with a single HbA1c test. This value may not accurately reflect alterations in metabolic control over time.

However, patients in the present study on average had diabetes for more than 30 years and were most likely to be in a stable condition. A positive relationship was noted between HbA1c and laser-treated retinopathy ($r=0.2$, $P<0.01$), indicating that the measured HbA1c was a biomarker for glucose dependent complications. The strength of the studies included the large sample size and population-based design, which included a matched control group (Papers I–III). The study included well-known and validated instruments, which facilitated comparison of the present results to those of other studies.

CONCLUSION

1. The prevalence of UEIs is higher and causes more activity limitations in patients with T1D than in controls. The overall risk profile for different impairments varies, suggesting heterogeneous etiologies.
2. The IGF system is dysregulated in T1D and cannot be reversed by subcutaneous insulin administration. Preserved endogenous insulin secretion seems to counteract these alterations. The UEIs are not significantly related to the IGF system.
3. The HRQOL is significantly lower in patients with T1D than in controls. A reduced HRQOL was associated with shoulder and hand impairments. Patients with T1D have a higher frequency of sick leave than controls, and a common reason for this is musculoskeletal impairment.
4. Self-reported impairments of the shoulder, hand, and finger show high reliability and are associated with the findings of clinical examinations. Self-reported shoulder impairments, reduced grip force and previous surgery for CT or TF are associated with several clinical impairments and might be used to identify individuals at risk.

FUTURE ASPECTS

New questions arose on completion of our studies. Where do we go from here?

As UEIs are very common findings, how do we handle them in the clinic?

Disability can be extensive in patients with T1D compared with controls. Furthermore, female sex, a longer diabetes duration, and insufficient glycemic control are associated with a higher risk of disability. Our results show that self-reported disabilities are consistent with clinically determined disabilities. We identified key questions from the questionnaire that could be easily used in the clinical setting to identify patients with extensive disability. These key questions need to be tested in the clinical setting and should also be applied for patients with a shorter duration of diabetes.

Patients with T1D and prevalent disabilities, or those at high risk of developing disabilities need to be better identified and offered interventions from a multi-professional team focused on the disability. Interestingly, physical exercise has been receiving increased attention and is highly recommended for patients with diabetes, because of its overall health benefits and effects in improving glucose management¹³⁵. In addition, there has been increased focus on flexibility exercises, in order to improve the range of motion around joints, as LJM is more common with increasing age and diabetes duration¹³⁵.

The questions in the study-specific questionnaire were constructed by experienced clinicians. However, there is a need for further studies based on the patient's perspective. Qualitative research studies, including those considering focus groups and the patient's perspective regarding the impact of T1D on everyday life can be further explored and analyzed. This may add important details to facilitate the development of clinically relevant questionnaires.

There is also a need for longitudinal follow-ups of disability and glycemic control in T1D cohorts, preferably commencing at the time of T1D diagnosis. This could offer possibilities to analyze the outcomes of glycemic control together with disability over time. The next steps would entail the analysis and/or identification of patients at risk for even worse disabilities. Cohort studies, with a longitudinal design, can also constitute a base for further studies of evidence for rehabilitation interventions in T1D. Another important way to gain further knowledge, as well as achieve greater awareness of clinical routines would be to include questions on UEIs in the national diabetes registry and include yearly follow up data with national coverage.

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all the people who have contributed to these studies and in particular:

All the patients and controls for their participation and collaboration.

Anna Spångeus, my main supervisor, who convincingly guided and encouraged me to be professional and do the right thing even when the road got tough. Without her persistent help, explicit tutoring, and computer skills, the goal of this project would not have been realized.

Hans Arnqvist, for generously sharing his expertise in diabetes and IGF research. His enthusiasm, constructive criticism, and discussions have been invaluable throughout these studies.

Ingrid Thyberg, for her expertise, inspiring comments, and discussions, from the start of this project (my take home message here: structure is important), which I will never forget.

Margareta Bachrach-Lindström, for invaluable discussions and help with the health-related quality of life research. Always understanding and encouraging!

Torbjörn Lindström, who was a great colleague in every aspect. You taught me so much and introduced me to the field of clinical and diabetes research. I will never forget you.

Björn Lindström, for great efforts with computer work at the very beginning of our studies.

Christina Hedman, for including me in your diabetes research group and for encouraging me during difficult times.

Anna-Kristina Granath, for skilful performance of laboratory analyses.

Bertil Ekman, for sharing excellent skills in the mysterious field of endocrinology, for his never-ending enthusiasm, and encouragement along the way. The chocolate was always very appreciated!

Marit Svensson and Sofia Sjöberg, for all help with study IV.

All the incredible diabetes nurses at the Diabetes Department, for grateful collaborations during the years.

Elzbieta Partyka-Rut, for being Ela, a great colleague, and my friend.

My husband David, my children Carl and Christine. They kept me going, and this work would not have been possible without their support and unconditional belief in me.

My parents, Christer and Barbro Jonasson, for always believing in me. I love you.

Financial support was obtained from County Council of Östergötland; Stiftelseförvaltningen (LIO-483521) and Forsknings-ALF (LIO-608721, LIO-690101, LIO-795171) as well as from the Medical Research Council of Southeast Sweden; FORSS (FORSS-155831, FORSS-312821 and FORSS-795171). Their financial supports were truly appreciated and without it this project could not have reached its goal.

Papers

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FACULTY OF MEDICINE AND HEALTH SCIENCES

Linköping University medical dissertations, No.1728, 2020
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