Shoulder and hand diagnoses, stiffness and associated disability of the upper extremities in patients with type 1 diabetes for more than 45 years.

The Dialong study.

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During my regular clinical work at the outpatient clinic for musculoskeletal patients at Oslo University Hospital, Ullevål (OUHU) in 2014 I was contacted by Tore Julsrud Berg from the Department of Endocrinology, Morbid Obesity and Preventive Medicine at OUHU. He wondered if I knew anyone experienced in working with patients with frozen shoulder. At that time, I conducted a study concerning frozen shoulder and after a short talk in my office he invited me into his exciting, well planned and multifaceted study concerning persons with very long-term type 1 diabetes mellitus, the Dialong study. During this first talk I also learned about three new concepts for me in musculoskeletal medicine: cheiroarthropathy, limited joint mobility and Prayer sign. During the following three years, I have learned a lot more about diabetes from Tore and also about how to organize complex research projects in a friendly and including way and not least about being open and productive, but still precise in methodological and scientific discussions. Without Tore’s special interest in the musculoskeletal complications of diabetes the present papers and this thesis would not exist.

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ABBREVIATIONS

AGEs - Advanced glycation end products
AROM - Active range of motion
AUSCAN - Australian/Canadian scale for self-reported hand pain, disability and stiffness
CTS - Carpal tunnel syndrome
DD - Dupuytrens disease
DM1 - Type 1 diabetes mellitus
DISH - Diffuse idiopathic skeletal hyperostosis
FFD - Fingertip-to-floor distance
FS - Frozen shoulder
HbA1c - Glycated haemoglobin A1c
K-L classification - Kellgren-Lawrence classification
LJM - Limited joint mobility
MOLD - Methyl-glyoxal-lysine dimer
MRI - Magnetic resonance imaging
NDC - Norwegian Diabetics Center
NRS - Numeric rating scale
OA - Osteoarthritis
OUHU - Oslo University Hospital, Ullevål
OWD - Occiput-to-wall distance
PROM - Passive range of motion
PROMs - Patient reported outcome measures
QuickDASH - Short form of the Disabilities of the Arm, Shoulder and Hand (DASH), a PROM
ROM - Range of motion
S-P classification - Samilson-Prieto classification
S-PA classification - Samilson-Prieto Allain classification
SR - Systematic review
STROBE - Strengthening the Reporting of Observational Studies in Epidemiology
TF - Trigger finger
VAS - Visual analog scale
LIST OF PAPERS

Paper 1.


Paper 2.


Paper 3.


Paper 4.


Paper 5.

SUMMARY

The aim of the thesis was to estimate the prevalence of musculoskeletal disorders and associated pain, stiffness and disability in a cohort of patients with type 1 diabetes mellitus (DM1) of more than 45 years’ duration compared with a control group in a cross-sectional study. We also explored the association between disability, stiffness, long term HbA1c and advanced glycation end products.

Subjects and methods. One hundred and two patients with diabetes of a mean duration of 50.6 years, mean age 61.9 years, and 73 diabetes-free persons, mean age 62.6 years, were examined. The subjects completed a questionnaire, went through a standardized clinical examination and had shoulder and hand x-rays, blood samples and a skin biopsy taken. We collected historical HbA1c data from patient files to evaluate the glycaemic burden. The assessors were blinded for group affiliation.

Results. In paper 1 we found the point prevalence of frozen shoulder in the DM1 group to be 59% with a 76% lifetime prevalence. The DM1 group had higher shoulder disability scores associated with the historical HbA1c levels. In paper 2 a higher prevalence of radiological glenohumeral osteoarthritis (OA) was observed in patients with DM1 (35% vs 14%), not associated with shoulder pain or long-term glycaemic burden. In paper 3 we found a higher prevalence of radiological glenohumeral OA in the diabetes group for two of three different classification systems (30 to 44% vs 17 to 26%) with moderate inter-rater agreement. Higher prevalence was not observed for moderate to severe radiological OA and clinical OA. We found no association between radiological and clinical OA. In paper 4 DM1 was not associated with radiological hand OA, but with hand pain, disability and stiffness. In paper 5 we estimated a higher lifetime prevalence of hand and shoulder diagnoses in DM1 and a higher prevalence of hand, shoulder and back stiffness associated with long term HbA1c. Back stiffness was associated with two of eight advanced glycation end products (AGEs) examined.

Limitations. We examined 75% of the eligible group with a smaller number of controls. The number with moderate and severe OA was too low for any inference. The reliability of radiological glenohumeral OA was moderate and the reliability was not examined for clinical procedures. The AGEs measured in skin collagen may not be representative for joint capsule collagen.

Conclusions. Patients with very long term DM1 had higher disability scores and more stiffness of the shoulders and hands compared with controls. High point and lifetime prevalence of frozen shoulder and hand disorders were associated with the long term HbA1c. The prevalence of radiological glenohumeral OA was increased, but not associated with shoulder pain and long term HbA1c levels.

Clinical interpretation. The present studies suggest that assessment of musculoskeletal pain and disability should be addressed in future diabetes guidelines.
1. INTRODUCTION

1.1 Diabetes mellitus

Diabetes mellitus is characterised by increased levels of glucose in the blood. The most common types are type 1 and type 2 diabetes mellitus. Type 1 diabetes mellitus (DM1) is caused by an autoimmune-mediated destruction of insulin-producing pancreatic β cells. The symptomatic onset is mainly in childhood or adolescence, but may also occur in higher age often due to a more gradual loss of β cells over years (5).

Genetic predisposition is shown to increase the risk of DM1 substantially. Twin-studies demonstrate a 25-50% risk for diabetes in a monozygotic and 3-10% in a dizygotic twin if the other twin develops DM1 (6).

A model for the natural development of DM1 integrates the genetic susceptibility with environmental factors that may contribute to development of clinical disease. The genetic predisposition does not fit any simple pattern of heritage and is considered complex. Many genes are identified with susceptibility to the disease. The Human Leukocyte Antigen (HLA) complex is regarded as most important, but over 50 loci have been associated with DM1 (7). A ten-fold increase in risk of developing DM1 from 0.5% in the general population is reported with a first-degree relative with DM1 (6).

Environmental factors may trigger or protect against the immune response responsible for the β cell destruction. A recent Norwegian study suggests that a low-grade enteroviral infection in the pancreatic islets contributes to disease progression in humans (8). High concentrations of islet autoantibodies are shown early in childhood in children who develops DM1 (9). Such autoantibodies may contribute to the β cell destruction and when the β cell mass is under a certain level most persons progress to overt disease after a shorter or longer phase with pathological glucose metabolism and increased glucose fluctuations (figure 1) (5).

Figure 1. Model of the pathogenesis of type 1 diabetes. With permission, from Atkinson (5).
The incidence rates are reported stable in Norway for persons under 15 years (figure 2) (10). The overall incidence rate in the total population was 33 per 100,000-person years and was also found stable over time (11). 31,515 individuals (0.64% of the population) in Norway used insulin only for blood glucose control in 2010.

![Figure 2. Yearly observed type 1 diabetes incidence rates per 100,000 with 95% CIs for children (under 15 years) in Norway during 1989–2012. With permission, from Skrivarhaug (10).](image)

Patients with DM1 have reduced life expectancy compared to the diabetes free population. The gap has decreased the last 30 to 40 years. Studies from Sweden show reduced mortality rates from cardiovascular diseases most likely related to a combination of an increased emphasis on integrated care of patients with chronic disease and improved patient education in disease management. The authors point out improved management of specific cardiovascular risk factors such as hypertension, elevated levels of LDL-cholesterol and glycated haemoglobin (HbA1c) as important for the cardiovascular risk reduction (12, 13).

The Diabetes Control and Complications Trial (DCCT) was conducted to investigate if complications of DM1 could be reduced by lowering levels of glycaemia safely and as close to the normative range as possible (14). The Epidemiology of Diabetes Interventions and Complications (EDIC) observational follow-up study reported the durability of the DCCT effects on the more advanced stages of diabetes complications including cardiovascular disease. These studies showed that reduced glycaemia close to the nondiabetic range reduced microvascular and cardiovascular complications (15).
1.2 Musculoskeletal complications in diabetes

Although mortality from type 1 diabetes is still high (OR 3.5), life expectancy for patients with DM1 has increased due to improved diabetes treatment the last 30-40 years (16). Thus, there are increasing numbers of persons living almost a normal life-span with DM1. Currently there are no recommendations for routine clinical examination and treatment for musculoskeletal complications in national or international diabetes guidelines (17, 18). This may accommodate an under-estimation of the conditions by health care practitioners. In the shoulder and hand diagnoses have been reported to be associated with both type 1 and type 2 diabetes. Furthermore, diabetes is associated with musculoskeletal pain and may have a negative impact on the quality of life (19-22). Shoulder and hand diagnoses have been associated with the duration of diabetes, age, gender, microvascular complications and to varying degree glucose control (20-23). Still there are only a few reports on the prevalence of musculoskeletal diagnoses in long-term DM1 and estimates of prevalence lacks completely in disease duration beyond 31 years.

1.2.1 Epidemiology

Banon and Isenberg performed a literature search concerning musculoskeletal conditions reported in diabetes in the PubMed database between 2003 and 2011 (19). The study of Cagliero et al. (21) in patients with disease duration of DM1 of 22 years was included in this review. In addition, there are two observational studies of patients with DM1 focusing on musculoskeletal problems. Before 2003 Arkkila et al. examined patients with mean disease duration of 18 years (22) while Larkin et al. published a large study in 2014 with mean disease duration of 31 years (20).

Banon and Isenberg found a prevalence of frozen shoulder (FS) between 7 and 30% with no predominance in diabetes type while Arkkila et al. found a 10% and Larkin et al. showed a 31% prevalence in DM1. Increased prevalence was not reported for any other shoulder diagnoses. In non-diabetes populations reported prevalence range from 11 to 21% (24-26).

In the hand Banon and Isenberg found a prevalence of Dupuytrens disease (DD) between 5 and 21% compared to 3 to 9% in the general population, a prevalence of Trigger finger (TF) up to 20% in DM1, a prevalence of 5 to 25% in mixed diabetes populations versus 0.5 to 15% in the general population for Carpal tunnel syndrome (CTS) and an 8 to 58% prevalence for Limited joint mobility (LJM) of the hands in DM1 versus zero to 26% in the general population.

The prevalence of these disorders in studies on long term DM1 are listed in table 1.
<table>
<thead>
<tr>
<th>Study</th>
<th>Mean age (SD)</th>
<th>Duration of disease (SD)</th>
<th>Frozen shoulder disease</th>
<th>Dupuytrens disease</th>
<th>Trigger finger</th>
<th>Carpal tunnel syndrome</th>
<th>Limited joint mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arkkila (1996)</td>
<td>33 (10)</td>
<td>18 (10)</td>
<td>10</td>
<td>20</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>Caglieri (2002)</td>
<td>40 (11)</td>
<td>22 (11)</td>
<td>16</td>
<td>20</td>
<td>20</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Larkin (2014)</td>
<td>52 (7)</td>
<td>31 (5)</td>
<td>31</td>
<td>9</td>
<td>28</td>
<td>30</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 1. Prevalence of frequent reported diagnoses in shoulders and hands in studies reporting on long-term DM1.

Banon and Isenberg did not find many studies reporting bothersome conditions from other parts of the musculoskeletal system. Diffuse idiopathic skeletal hyperostosis (DISH) of the spine was mentioned in three studies with conflicting evidence of increased prevalence. One study included specific foot problems as diabetic neuropathic osteoarthropathy (Charcot foot) associated with polyneuropathy. Banon and Isenberg did not report the prevalence of osteoarthritis in any joints.

1.2.2 Possible mechanisms for musculoskeletal pain

Little is known about the causal relationship between diabetes and musculoskeletal pain. Most studies show an association with the long term HbA1c. Possible pathways for an association between diabetes and osteoarthritis in non-weight bearing joints are proposed (27). Diabetes may cause a low-grade systemic inflammation which may contribute to joint inflammation and pain (27). Diabetic neuropathy can contribute to pain and is often present in patients with long-term diabetes (28).

Formation of advanced glycation end products (AGEs) in diabetes may also contribute to OA and pain by various mechanisms affecting collagen tissue and chondrocytes (29).

1.2.2.1 Advanced Glycation End products

There are several theories as to how chronic hyperglycaemia can lead to micro- or macrovascular disease in diabetes, including the advanced glycation end products (AGEs) theory. The AGEs are known to have various chemical, cellular and tissue effects which may be implicated in diabetic vascular complications. The production of AGEs is increased in diabetes and may affect cells by three mechanisms (30). The mechanisms are; modification of intracellular proteins, increased extracellular matrix production and extracellular modification of circulating proteins like albumin which may bind to and activate AGE-receptors and cause production of inflammatory cytokines and growth factors which further may cause vascular pathology. AGEs constitute of a heterogenous group of molecules formed by the non-enzymatic reaction of reducing sugars with amino acids, lipids and nucleic acids. Diet may act as an exogenous source of AGEs possibly influencing the circulating levels of AGEs. Balance in the circulating levels is usually obtained through endogenous formation, oral intake and
the catabolism of AGEs in the kidneys and tissue degeneration. This homeostatic system may be altered by diabetes, but also by elevated oral intake or failure of renal excretion (31, 32).

Some of the AGEs are known to cross-link to collagen and thereby impairing its properties resulting in increased collagen stiffness (33). This process is therefore postulated as an underlying mechanism for musculoskeletal disorders and stiffness developing with age and in diabetes (19, 20, 33). There is a lack of studies on this association, and the findings have been inconsistent (34). The AGEs suspected to cross-link to collagen is mainly glucosepane and to a lesser degree also pentosidine and methylglyoxal-lysine dimer (MOLD) (34).

1.2.3 Diagnoses in the shoulder

<table>
<thead>
<tr>
<th>ICD-10 diagnosis with description</th>
<th>Symptoms</th>
<th>Diagnostic criteria</th>
<th>Imaging that may increase diagnostic accuracy</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>M75.4 Subacromial pain syndrome</td>
<td>Pain in the shoulder and proximal lateral upper arm exacerbated by activity</td>
<td>Typical pain and positive impingement test and pain with isometric abduction or external rotation</td>
<td>None</td>
<td>(35, 36)</td>
</tr>
<tr>
<td>M79.11 Myalgia in shoulder muscles</td>
<td>Diffuse pain outside the glenohumeral joint localised over muscles</td>
<td>Negative specific tests, pain when palpating muscles</td>
<td>None</td>
<td>(26)</td>
</tr>
<tr>
<td>M75.0 Frozen shoulder (Adhesive capsulitis)</td>
<td>Pain in the shoulder exacerbated by activity. Feeling of stiffness.</td>
<td>Reduced passive range of glenohumeral motion in passive ext. rot. + at least one of active flexion or passive abduction &gt; 2 SD from normative value</td>
<td>None</td>
<td>See below (1)</td>
</tr>
<tr>
<td>M75.1 Full thickness rotator cuff tear</td>
<td>Pain in the shoulder. Occasional feeling of weakness</td>
<td>Positive impingement test and weakness with isometric abduction or external rotation</td>
<td>MRI and US</td>
<td>(26, 36, 37)</td>
</tr>
<tr>
<td>M19.8 Acromioclavicular (AC) joint osteoarthritis</td>
<td>Pain on top of shoulder, over the AC joint</td>
<td>Pain with joint palpation. Osteoarthritis on X-ray, US or MRI</td>
<td>X-ray</td>
<td>(26, 38)</td>
</tr>
<tr>
<td>M19.0 Glenohumeral joint osteoarthritis</td>
<td>Pain in the shoulder. Occasional feeling of stiffness</td>
<td>Osteoarthritis on X-ray or MRI</td>
<td>X-ray</td>
<td>(26)</td>
</tr>
</tbody>
</table>

Table 2. The most common shoulder diagnoses with diagnostic criteria.
Most diagnoses in the shoulder are based on the history and clinical examination alone and there is no objective gold standard to compare to for the most common diagnoses (39, 40). The diagnoses osteoarthritis and full thickness rotator cuff tears require corresponding findings on imaging (41). We used a standardised diagnostic routine to identify the point prevalence of musculoskeletal diagnoses (appendix 1). The diagnoses were based on clusters of patient-reported symptoms as stated in the literature and one or more simple clinical tests shown to have moderate to good inter- and intra-tester reliability (table 2 and table 3).

<table>
<thead>
<tr>
<th>Examination</th>
<th>Measurement</th>
<th>Intra-rater reliability (ICC)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain on active abduction</td>
<td>VAS 1-10</td>
<td>sensitivity/specificity 0.73/0.81</td>
<td>(36)</td>
</tr>
<tr>
<td>AROM flexion</td>
<td>Degrees 0-180</td>
<td>0.53 (0.21-0.82)</td>
<td>(42)</td>
</tr>
<tr>
<td>AROM external rotation</td>
<td>Degrees 0-100</td>
<td>0.65 (0.36-0.88) (K)</td>
<td>(42)</td>
</tr>
<tr>
<td>Hand-Behind-Back</td>
<td>Centimetres from C7</td>
<td>0.39 (0.08-0.75)</td>
<td>(42)</td>
</tr>
<tr>
<td>PROM external rotation</td>
<td>Degrees 0-100</td>
<td>0.88, 0.90, 0.87-0.93</td>
<td>(43, 44) (45)</td>
</tr>
<tr>
<td>PROM abduction</td>
<td>Degrees 0-120</td>
<td>0.84, 0.87, 0.85-0.98</td>
<td>(43, 44) (46)</td>
</tr>
<tr>
<td>Isometric external rotation</td>
<td>Pain, loss of force</td>
<td>0.37-0.90 (K)</td>
<td>(47)</td>
</tr>
<tr>
<td>Isometric abduction</td>
<td>Pain, loss of force</td>
<td>0.30-0.94 (K)</td>
<td>(46)</td>
</tr>
<tr>
<td>Force external rotation</td>
<td>Newton</td>
<td>Na</td>
<td></td>
</tr>
<tr>
<td>Force abduction</td>
<td>Newton</td>
<td>Na</td>
<td></td>
</tr>
<tr>
<td>Impingement sign</td>
<td>Negative or positive</td>
<td>0.18-0.91 (K), 0.38 (K)</td>
<td>(46) (48)</td>
</tr>
<tr>
<td>AC-joint palpation</td>
<td>Negative or positive</td>
<td>sensitivity/specificity 0.73/0.10, 0.36/0.73</td>
<td>(38) (40)</td>
</tr>
</tbody>
</table>

Table 3. The diagnostic tests used for the shoulder diagnoses with reported intra-rater reliability or sensitivity/specificity. VAS=Visual analog scale, AROM=active range of motion, PROM=passive range of motion, AC-joint=acromioclavicular joint. Values for intra-rater reliability with Cohens kappa (K) or Intraclass correlation coefficient (ICC).

1.2.3.1 Frozen shoulder

Frozen shoulder, also termed “adhesive capsulitis”, is a common source of shoulder pain and disability and especially in long-term DM1. In general, frozen shoulder is most prevalent from 45 to 65 years of age and affects women slightly more often than men. The lifetime prevalence in general practice is reported to be 11 to 21% (24, 25), but the diagnostic criteria used was not described properly. The percentage of patients with frozen shoulder was 11% in a one-year cohort of shoulder patients in specialist care (26). The diagnostic criteria for frozen shoulder are debated. The etiology
and pathophysiology of the condition is poorly understood, and a specific cause of the disease has not been found despite several studies on potential underlying pathology and pathophysiology (49-51). In a systematic review from 2016 Ryan et al. assessed 3558 papers and included 13 studies (49). Eight of the studies reported on radiological and five on histological findings. From the radiological studies changes in and around the anterior shoulder joint capsule (the coracohumeral ligament, the axillary fold and the rotator interval) were frequently found on magnetic resonance imaging (MRI). A later study supports this and implies that changes in the axillary recess mainly restrict abduction and flexion of the arm, while changes in the rotator interval and anterior capsule mainly restrict rotation (52). However, the correlation between MRI findings and clinical impairment in patients with adhesive capsulitis is reported to be weak (53). The histological studies were inconclusive but reported associations with immunological, inflammatory and fibrotic changes (49). A study of Hand et al. from 2007, not included in the systematic review, concluded that a chronic inflammatory response with fibroblastic proliferation, possibly immunomodulated, was the most likely pathophysiological mechanism in frozen shoulder (50).

Because of the limited radiological diagnostic validity most studies on frozen shoulder rely on clinical criteria for the diagnosis. A combination of clinical symptoms and findings on examination was proposed already in 1872 by Duplay (54) which called the condition “Periarteritis of the humeroscapular joint”. In 1934 Codman introduced the name “Frozen shoulder” in his book (55) and described the disease as a painful restriction of range of motion of the shoulder in the presence of normal plain x-rays. Neviaser observed quite severe adhesions in the shoulder capsule during operations. He analysed microscopic sections of the capsule and found reparative inflammatory changes and therefore proposed the name “Adhesive capsulitis” as descriptive of the pathology of frozen shoulder (51). He described the clinical picture as characterized by pain and limitation of motion in abduction, and internal and external rotation. Later numerous authors have used this as inclusion criteria for observational and randomized controlled trials. The diagnostic criteria used varies substantially, but do always include a painful shoulder and restricted range of shoulder motion in one or more planes for active or passive movements.

In order to evaluate the diagnostic criteria used for frozen shoulder, we did a literature search in Pubmed in March 2017 for the terms “Frozen shoulder” and “Adhesive capsulitis” in studies published after year 2000. We identified 939 titles and extracted 150 abstracts. 46 articles were collected in full text, 22 of these used clear diagnostic criteria. Sixteen of the studies compared range of motion of the affected shoulder with the unaffected. Ten studies acquired a certain percentage reduction in one or more directions. Most common was a 50% reduction (6 studies), then 25% (3 studies) and 30% (1 study). Eight studies required at least 30 degrees loss of movement in two or
more directions, while four studies had other criteria. The impact of the various criteria on normative values for range of motion is shown in Table 4.

Most studies on frozen shoulder included only unilateral cases and compared the affected shoulder to the unaffected. All studies required shoulder pain for the diagnosis. Based on these criteria the diagnosis of frozen shoulder cannot be made in patients without shoulder pain.

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Normative</th>
<th>2 SD</th>
<th>-2 SD</th>
<th>-30°</th>
<th>-50%</th>
<th>-25%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ext. rotation</td>
<td>68</td>
<td>32</td>
<td>36</td>
<td>38</td>
<td>34</td>
<td>51</td>
</tr>
<tr>
<td>Abduction</td>
<td>85</td>
<td>38</td>
<td>47</td>
<td>55</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>AROM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flexion</td>
<td>160</td>
<td>20</td>
<td>140</td>
<td>130</td>
<td>80</td>
<td>120</td>
</tr>
<tr>
<td>Ext. rotation</td>
<td>55</td>
<td>32</td>
<td>23</td>
<td>25</td>
<td>28</td>
<td>41</td>
</tr>
</tbody>
</table>

Table 4. The change the most frequent used diagnostic criteria cause on the range of motion from the normative values in different directions. -2SD: reduced 2 standard deviations, -30°: reduced 30°, -50% and -25%: 50% and 25% reduced range of motion respectively. PROM=passive range of motion. AROM=active range of motion.

The natural course of frozen shoulder

The natural course of frozen shoulder is commonly divided into phases with distinctive, but overlapping characteristics (figure 3) (56-58):

- Phase 1: The painful phase, usually lasting between two and nine months. Insidious development of severe shoulder pain that is worse at night and gradually increasing shoulder stiffness.
- Phase 2: The “freezing” phase, usually lasting between four and twelve months. Stiffness in shoulder motion predominates and can be severe. A gradually decrease in pain is regularly seen.
- Phase 3: The resolution or recovery phase can last between 5 and 24 months and is predominantly pain free. There is a gradual return of movement.

Figure 3. A model of the natural course of frozen shoulder. Pain intensity from 0 to 100 (100 maximal pain) and loss of external rotation in degrees (secondary axis). The three phases of the disease in top boxes.
Most of the previous studies have focused on frozen shoulder in phase 1 or 2 because of the bothersome pain. Fewer have looked at the natural course. Reeves is often referred to as the establisher of the three phases of the disease (59). He followed 41 patients (42-63 years, 54% women) closely for five years and some up to ten years. He found the painful period to last 10 to 36 weeks (two to nine months), the stiff period with decreasing pain to last four to 12 months and the recovery period with less or no pain to last for 12 – 42 months. The mean duration of the disease was 30 months. After five years, he found that 16 of the 41 patients were left without reduced shoulder movement and 22 patients with some reduction of shoulder movement, but without functional limitations. Only three patients (7%) were left with both restrictions in shoulder movement and functional limitations. These three patients had 40-60% reduction in both internal and external rotation and abduction.

Diercks et al. followed 77 patients with frozen shoulder prospectively every three months for 2 years (60). The mean age was 51 years with 61% women and the disease duration was 5 months (mean) at baseline. One group was treated with supervised neglect (natural course) and improved steadily. After 1 year, 64% of this group had little or no disability and after 2 years, the number was 89%.

Kivimäki at al. followed 60 persons with frozen shoulder in a control group receiving home exercises only as part of a RCT (61). The mean age was 53 years with 65% women and with a disease duration of seven months at baseline. During four follow-ups over one year, pain in the control group were reduced from 6.4 to 2.2 on a scale from 0 to 10 (worst) and passive external rotation increased to the level of normative data (from 18 to 61 degrees). They imply a shorter natural course than described earlier in the literature.

The development of the disease from the start and until the baseline examination (0 on x-axis, figure 4) is not known in any of the studies, but it looks like pain and loss of passive external rotation follow the same trajectory and has a benign outcome for most the patients after one and two years without treatment (figure 4).
Figure 4. The natural course of pain (0 to 100, 100 worst) and loss of external rotation (degrees) in frozen shoulder. Zero on x-axis represent duration of the disease at baseline in the studies (5 and 7 months). Data combined from Kivimäki et al. (61) and Diercks et al. (60) by Juel NG.

**Shoulder range of motion**

In general, measurements of ROM are shown to have poor to moderate inter- and intra-tester reliability whether manual or electronic goniometers or visual inspection are used (46, 62). When measurements of active ROM are done in a painful shoulder the reliability may be even poorer (63). However, a recent study on persons with painful frozen shoulder showed very good to excellent inter-tester reliability for passive internal and external rotation and abduction in both painful and pain free shoulders measured with an inclinometer (64). The study showed very high reliability calculated with the Intraclass correlation coefficient (0.83-0.91) with measurement errors for abduction of 5.9° to 7.2° and 4.5° to 6.2° for external rotation using the within-subject standard deviation between the two testers. For the hand-behind-back test measurement errors of 1.1 and 2.1 cm was found. Another report on the reliability of glenohumeral ROM measured standing found active flexion (SD) to be 151° (8) with an intra-rater ICC of 0.63, a standard error of measurement (SEM) of 5° and a minimal detectable change (MDC) of 14° (65). For passive external rotation they found an ICC of 0.94, SEM of 7° and MDC of 11°. The SEM express the amount of change needed to exceed the error of the measurement itself and allows for the determination of when an observed change is greater than the measurement error itself (66). The MDC can be used to assess the minimal magnitude of change required to be 95% confident that the observed change between two tests reflects true change and not measurement error. The MDC can be calculated as: $1.96 \times \text{SEM} \times \sqrt{2}$ (67).
Normative data for active and passive ROM measurements are used in the present study (table 5) (46, 65). The numbers were not age adjusted because of the small effect of age showed by Macedo et al. (68).

<table>
<thead>
<tr>
<th>Direction of movement</th>
<th>Normative values, °(2SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active flexion</td>
<td>160° (20)</td>
</tr>
<tr>
<td>Active external rotation</td>
<td>55° (32)</td>
</tr>
<tr>
<td>Passive external rotation</td>
<td>68° (32)</td>
</tr>
<tr>
<td>Passive abduction</td>
<td>85° (38)</td>
</tr>
</tbody>
</table>

Table 5. Normative values for glenohumeral range of motion in ° (2SD).

**Shoulder muscle strength**

Shoulder muscle strength may be measured in different ways. Isometric strength testing is frequently used in medicine and especially in the extremities. The purpose of an isometrics test is to get a reliable measure of the individuals’ strength in the particular position tested and to compare the obtained values to normative values, change in the individual over time or to the opposite side. The positioning of the limb is typically done to be able to test an individual muscle as specific as possible without co-contraction from other muscles. A basic protocol for isometric strength testing was developed in the seventies (69) and this protocol is still widely used. Recently the reliability of isometric testing with a hand-held dynamometer in external and internal rotation in the shoulder is found to be excellent (70). When conducting isometric testing, a number of factors ought to be considered to avoid biased results:

- Equipment used to make the measurements
- Instructions given to the person tested
- Duration of the measurement period
- Person’s posture during the test
- Length of the rest between attempts
- Number of attempts a person is given for each test
- Tested person’s physical and mental state at the time of testing
- Type of postural control used during the tests
- Environmental conditions during the test

In the current study, we addressed the relevant factors in this list to standardize the measurements as much as possible.

**1.2.4 Diagnoses in the hand**

A population-based cohort study from Taiwan showed an increased risk of developing hand diagnoses for patients with mixed types diabetes mellitus compared to diabetes-free persons (71).
Hazard ratios for developing disease were significant and between 1.35 and 1.83 over a nine-year period for the hand syndromes described below. Hand syndromes may be disabling for patients with long-term diabetes (72). Studies of the risk for developing hand diagnoses in DM1 only is not available.

<table>
<thead>
<tr>
<th>ICD-10 diagnosis with description</th>
<th>Symptoms</th>
<th>Diagnostic criteria</th>
<th>Supplementary investigations that might increase diagnostic accuracy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>G56.0 Carpal tunnel syndrome</td>
<td>Paraesthesia/pain in the median nerves sensory area. Sensory loss and weakness of the thenar muscles. Provocation of symptoms by sleep or hand work as well as mitigation of symptoms by shaking the wrist or change hand position.</td>
<td>Typical paraesthesia or pain. Loss of skin sensation or force in m. opponens or m. adductor at neurological examination and positive Phalen’s sign may strengthen the diagnosis, but is not necessary.</td>
<td>Nerve conduction survey, ultrasonography and magnetic resonance imaging.</td>
<td>(73, 74)</td>
</tr>
<tr>
<td>M72.0 Dupuytrens disease</td>
<td>No symptoms in early phase. Nodules in the palm might be tender. Strings in the palm and fingers with flexion contracture in more severe cases.</td>
<td>Palpable nodules or strings in the palm. Loss of flexion may be present both in the metacarpophalangeal and interphalangeal joints.</td>
<td>None</td>
<td>(75, 76)</td>
</tr>
<tr>
<td>M65.3 Trigger finger</td>
<td>Locking of the finger in a flexed position and sometimes painful snapping with movement.</td>
<td>Locking of the finger in a flexed position and sometimes painful snapping with movement.</td>
<td>None</td>
<td>(19, 77)</td>
</tr>
<tr>
<td>Limited joint mobility</td>
<td>Non-painful hand stiffness caused by flexion contractures of the fingers and thickened skin.</td>
<td>A positive Prayer sign implies not being able to bring the palmar side of the hands and fingers into full contact when opposed.</td>
<td>None</td>
<td>(78, 79)</td>
</tr>
</tbody>
</table>

Table 6. The most common hand diagnoses in long-term DM1 with diagnostic criteria. Most hand diagnoses are based on clinical examination alone and there is no gold standard for the most common diagnoses. The diagnostic criteria for the most prevalent hand diagnoses in diabetes are detailed below (table 6).

1.2.4.1 Carpal tunnel syndrome

The typical symptoms are paraesthesia or pain in the median nerves’ sensory area (thumb and first two and a half fingers). Some patients complain of sensory disturbance in the whole hand or in the arm up towards the shoulder. A sensation of swelling in the hand occurs frequently. Permanent
sensory loss and weakness and atrophy of the thenar muscles are considered to be late signs (73, 80). The reported prevalence varies between 3% and 14% applying the diagnostic criteria described and the mean age at debut is 50 years. The condition is up to four times more prevalent in women and increases with age (73).

The syndrome is caused by a compromised median nerve function in the carpal tunnel at the wrist. The tissue pressure in the tunnel is increased in affected patients compared to asymptomatic persons and also varies with wrist position (80). Impaired microvascular circulation in the median nerve may lead to demyelination and destruction of axons. An increase of the connective tissue in the tunnel with reduction of the space may predispose for development of the syndrome (80).

The diagnosis may be difficult due to the variation of early symptoms. The American Academy of Neurology support diagnostic guidelines stating that the probability of diagnosis increases with the number of standard symptoms and provocative factors present (73, 74). In addition to the above symptoms they suggest provocation of symptoms by sleep or hand work to be important as well as mitigation of symptoms by shaking the wrist or change hand position. Clinical and supplementary examinations are available, but the clinical assessment is still considered to be the gold standard (73, 74, 80). In addition to a neurological examination the mostly used clinical tests are the Phalen’s test (provocation of paraesthesia by flexion of the wrist to 90 degrees for 60 seconds) and the Tinel’s sign (provocation of paraesthesia by tapping over the carpal tunnel). Large variation in sensitivity and specificity values are shown in studies evaluating these tests using nerve conduction velocities as the gold standard (80). The same considerations are valid for ultrasonography and magnetic resonance imaging.

Diabetes is reported to be a risk factor for carpal tunnel syndrome with an adjusted odds ratio of 1.69 (95% CI 1.45 – 1.96) (81). Hand function is regularly impaired (82).

1.2.4.2 Dupuytrens disease

Dupuytrens disease is a fibroproliferative disease of the palmar fascia of the hand with a reported prevalence of 22% in a Dutch population between 50 and 89 years, increasing with age (83). Only 4% of all the patients had flexion contracture of the fingers. Previous hand injury, excessive alcohol consumption and a family history, but not diabetes, are reported risk factors (83). In a meta-analysis of the prevalence in Western countries considerable variation was found ranging from 12% at 55 years to 29% at the age of 75 (76).

The condition is most often asymptomatic, especially in the primary nodular phase without flexion contracture (75). The diagnosis is based on palpation of nodules or strings in the palm. When
contracture is present loss of flexion may be measured both in the metacarpophalangeal and interphalangeal joints. No supplementary investigations are needed.

Banon and Isenberg suggests an increased prevalence with diabetes (19) but the prevalence they refer to are lower than in the Dutch studies above. For DM1 cohorts Arkkila et al. (23) reported 20%, Caglieri et al. (21) 20% and Larkin et al. (20) 9% respectively. These percentages suggest that Dupuytrens disease is not increased in DM1.

1.2.4.3 Trigger finger
The condition is caused by thickening of the peritendinous tissue giving catching of the flexor tendon with finger movement which is the diagnostic criteria. The symptoms are locking of the finger in a flexed position and sometimes painful snapping with movement. The reliability of the diagnostic criteria has not been reported. No supplementary investigations are needed. The condition is quite rare in the general population with reported prevalence of zero to two percent (19).

In DM1 considerably higher prevalence of 20% and 28% are reported (20, 21).

1.2.4.4 Limited joint mobility
The condition is characterized by non-painful hand stiffness caused by flexion contractures of the fingers and thickened skin. The condition is very rare in the general population and seems to be an almost disease-specific hand disorder for diabetes patients. It was first described in 1981 in children with DM1 by Rosenbloom (84) and in 1982 by Kennedy et al. They found a 36.5% prevalence increasing with the duration of diabetes (78). In a recent review prevalence from 8% to 58% were found in different diabetes populations. The etiology is unknown, but an association to both duration of diabetes and microvascular diabetic complications is reported (79). The main pathogenetic mechanism of joint stiffness is thought to be an increase of collagen cross-linking due to the non-enzymatic glycosylation of collagen with advanced glycation end-product formation (85). Limited joint mobility is known to be one of the earliest clinical signs of long-term complications in DM1 from publications in the 1980’s (84, 86). The prevalence seems to fall with improved standards of glycaemic control and a 50% reduction is shown over a 20-year period in the United Kingdom in 2005 (87).

The diagnosis is confirmed by the so-called Prayer sign in the hand (19, 20, 23, 79) and is measured as present or not. Usually the palmar side of the hands and fingers will have full contact when opposed. A positive Prayer sign is present when a subject is unable to do this because of flexion contracture of several finger joints (88). The reliability of the prayer sign is not reported to our knowledge.
1.2.5 Osteoarthritis

The Osteoarthritis Research Society International (OARSI) defines osteoarthritis (OA) as a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness (89).

The definition does not mention pain or disability more than as a possible end stage of the disease. The condition is both named osteoarthrosis and osteoarthritis (90).

OA is traditionally considered as a “wear and tear” disease through mechanical pathways. In the 1990s mediators like cytokines and prostaglandins that could lead to increased production of matrix metalloproteinases by chondrocytes were discovered. This introduced the inflammatory pathway for development of the disease with the synovitis as a crucial factor (90). Later studies have focused on systemic factors like obesity and obesity related metabolic factors, but the risk related to such factors are still unclear. Known risk factors include female sex, higher age, previous joint injury and genetic factors (91, 92). The genetics is complex and act through various pathways. Estimates suggest a heritability of 50% or more, indicating that half of the variation in susceptibility to disease in the population is explained by genetic factors (93). A recent meta-analysis of risk factor for radiographic progression of knee OA showed that baseline knee pain, presence of Heberden nodes, varus alignment, and high levels of serum markers (hyaluronic acid and tumor necrosis factor-alfa) predict progression while sex, knee injury, and quadriceps strength, among others, did not predict progression (94).

1.2.5.1 Osteoarthritis in the shoulder and hand

Most earlier studies regarding prognostic factors have focused on the knee joint which is affected by high mechanical loading (94). This contrasts with the joints in the shoulder and hand where the mechanical loads are lower.

In a Norwegian survey the prevalence of self-reported hand OA was 5% in men and 11% in women over 60 years (95) while the Norwegian prevalence of glenohumeral OA is unknown. In community dwelling populations in South Korea and Japan the radiological prevalence of glenohumeral OA is reported between 5 and 17% dependent of radiological classification system used (92, 96, 97).
Different classification systems for radiological glenohumeral OA exist based on shoulder x-rays (98). Traditionally the classification systems were developed to evaluate changes in the joint space in the knee according to cartilage destruction (the Kellgren-Lawrence (K-L) classification) (99). For non-weight bearing joints this basis for the classification is questioned and also because a linear reduction of the joint space with age is shown (100). Therefore, newer classifications like the Samilson-Prieto classification focus more on osteophyte formation in the circumference of the glenohumeral joint for mild and moderate OA than sole reduction of the joint space (101, 102). For the hand, the K-L classification is the most frequently used classification system which we also used in the present study.

1. The Kellgren-Lawrence (K-L) classification was first published in 1952 (103) and validated in 1957 (99) by J.H. Kellgren and J.S. Lawrence for evaluation of OA in the knee, hip, spine, foot and hand in miners. The classification is based on different radiological features including formation of osteophytes, periarticular ossicles, narrowing of the joint space, pseudocystic subchondral areas and altered shape of the bone ends.

2. The Samilson-Prieto classification (S-P) was originally developed in 1983 for the evaluation of dislocated shoulders by the two orthopaedic surgeons Robert L. Samilson and Victor Prieto (101). In this classification system focus is on osteophyte formation.

3. The modified Samilson-Prieto classification by Allain et al. (S-PA) was published in 1998 (102) to evaluate the long-term results after operating instable shoulders with the Latarjet procedure. It is very similar to the original Samilson-Prieto classification but focus only on osteophytes except in severe OA.

The reliability of the classification systems is investigated in several studies. Elsharkawi et al. evaluated the reliability of five versions of the Samilson-Prieto classification and reported almost perfect kappa values for intra-rater reliability for all versions (0.85 to 0.97) and substantial to almost perfect kappa value also for inter-rater reliability (0.79 to 0.94) (98). All patients included in this study had symptomatic OA and were surgical candidates. Brox et al. studied the reliability of the K-L and the Samilson-Prieto classifications in patients operated for shoulder instability and found the inter-rater reliability to be substantial with weighted kappa values of 0.72 for the K-L and 0.63 for the Samilson-Prieto classification for the unoperated shoulders (104). Kobayashi et al. calculated the intra-rater reliability for the Samilson-Prieto classification to 0.83 using the intraclass correlation coefficient and the inter-tester reliability was 0.80. The sample was community dwelling persons with mean age (SD) of 65 (11) years (96). Ilg et al. found substantial intra-tester kappa values for the S-P classification in both maximal external (40°) and internal (20°) rotation (0.62) for an experienced
observer versus poor and moderate (0.34 to 0.46) for a less experienced observer. The intra-tester kappa values were considerably lower (0.33 to 0.43 versus 0.05 to 0.55 respectively) for lower degrees of rotation for both observers (105).

Narrowing of the joint space is shown to decrease with increasing age and to be enhanced by osteoarthritis (100). The joint space width is not shown to correlate with the S-P grade or the size of osteophytes, shoulder pain or glenohumeral range of motion (106). The only factor reported to be related to measures of shoulder function was the size of the caudal humeral osteophyte which affected all movements (106).

1.2.5.2 Diabetes and osteoarthritis

A recent systematic review and meta-analysis by Louati et al. including mainly patients with type 2 diabetes reported an association between diabetes and OA (107). The metabolic syndrome with overweight, systemic inflammatory and adipose tissue related components may contribute to this association (90, 108) and a distinct diabetes mellitus OA phenotype has been proposed.

Diabetes and OA in the hand and shoulder

Few studies have explored the association between diabetes mellitus and hand or glenohumeral OA. Louati et al. (107) included two studies of the hand, showing an association between diabetes and hand OA particularly at younger ages. An association between a mixed diabetes population and erosive OA is reported recently (108). In contrast, another recent study did not identify type 2 diabetes as an independent risk factor for hand OA (109). Almost no research has been done in patients with DM1 (107).

Louati et al. did not include any studies on the shoulder (107) nor did Berenbaum in a report focusing on diabetes and OA (27). A systematic review from 2013 on rheumatological manifestations occurring in patients with diabetes mellitus did not mention OA (19) and neither do the large observational study of musculoskeletal problems in DM1 by Larkin et al. in 2014 (20). The association between diabetes and OA seems to be poorly evaluated with no studies on DM1.

1.2.6 Stiffness

Stiffness may be experienced either as pain when moving a joint or a body region, a feeling of loss of range of motion when moving or the physical sign of reduced range of motion. Stiffness may be difficult to measure precisely when pain is involved. In diabetes patients musculoskeletal problems may include muscle pain, joint pain or stiffness (110). Increased prevalence of shoulder (Frozen shoulder) and hand (Limited joint mobility) stiffness in DM1 is reported in numerous studies, while the evidence of a generalized body stiffness and stiffness in the neck and back is scarce (19-23).
Stiffness of the shoulder and hand have been described previously (see 1.2.3 and 1.2.4).

Stiffness in the spine may affect all sections. Diffuse idiopathic skeletal hyperostosis (DISH), also called Mb. Forestier, is described as calcification and ossification of ligaments and tendons predominantly in the thoracolumbar spine (19). The prevalence is reported to be 13% to 49% in type 2 diabetes populations versus 2% to 13% in the general population. Compared to a matched population with degeneration of the spine (spondylosis) the DISH patients had higher levels of uric acid and higher prevalence of type 2 diabetes (20% vs 9%) (111). A later study on DISH found minor differences in prevalence (12% vs 7%) in 133 patients with type 2 diabetes and 133 matched controls with a mean age of 63 years (112). Clinical measurement of stiffness in the spine is difficult because many joints are involved in spinal movement. From the work with patients with ankylosing spondylitis the Occiput-to-wall distance (OWD) is known to be a reliable estimate for cervical and thoracic spine extension (113). The fingertip-to-floor distance (FFD) is known as a reliable estimate for the overall flexibility in the lower back and hips. The method is validated and normative age adjusted values exist (114). The Schober test is a measure of movement in the lower back in forward bending. The test does not evaluate the overall flexibility in the lumbopelvic area. Intertester reliability is shown to be excellent (114).

1.2.7 Pain

Pain is the single most used item in published studies on shoulder disorders (115, 116). Pain is associated with disability (117) and high pain intensity predict poor outcome in shoulder patients in primary care (118).

Pain may be scored in diverse ways covering different aspects of pain sensation. Uni-dimensional scoring of pain intensity is usually done on a visual analog scale (VAS) or a numeric rating scale (NRS) ranging typically from zero to ten anchored by “No pain” for the lowest value and “Worst possible pain” for the highest value. Both VAS and NRS are shown to be reliable and valid for unidimensional assessment of pain intensity (119).

Different questions about pain are included in regional shoulder and hand specific patient reported outcome measures as the short form of the Disabilities of the arm, shoulder and hand score (Quick DASH) and the Australian/Canadian hand index (AUSCAN), both used in the present study.

1.2.8 Disability

Patient reported outcome measures (PROMs) of disability are commonly used in the functional assessment of patients with shoulder pain. Røe et al. identified 16 shoulder specific scores widely
used in research (116). The QuickDASH score is frequently used, evaluates the function of the entire arm and can be used both for shoulder and hand problems. QuickDASH has been translated to Norwegian, is validated in a Norwegian population and normative values from the general population exists (120, 121). The QuickDASH is found to have good psychometric properties (122, 123).

The AUSCAN has been developed to assess hand function. The score is in agreement with the consensus work of Outcome Measures in Rheumatology (OMERACT) recommending pain, physical function and patient global assessment as core measures for assessment of knee, hip and hand OA in clinical trials (124). The score has been translated to Norwegian and validated (125).

1.3 The need for research in the field

In the perspective of the increased life expectancy in type 1 diabetes, symptoms from the musculoskeletal system may be perceived as more bothersome as they seem to increase with age and disease duration (19-21, 126). To our knowledge, as outlined above, there is a paucity of reports on musculoskeletal disorders and disability in patients suffering from long-term DM1. Diagnoses like osteoarthritis in the glenohumeral and hand joints are not reported in DM1 populations at all earlier. The longest duration of DM1 studied is 31 years in patients with mean age of 52 years (20). Many patients have now lived with DM1 for more than 50 years and there are no studies on musculoskeletal disorders in this group.

There are also lack of studies describing the diagnostic criteria used for the reported diagnoses in DM1 populations in a transparent and scientific way.

The musculoskeletal topic is not mentioned in recent international or Norwegian clinical guidelines on diabetes (17, 18).

Taking the above-mentioned factors into consideration there is need for more research in this field to fill the knowledge gap concerning musculoskeletal problems in DM1 and especially in persons with very long duration of the disease. Our aim was therefore to study the prevalence of musculoskeletal disorders in long-term DM1 and to describe the accompanying disability in this patient group.

2. SPECIFIC AIMS OF THE STUDY

The overall aim of this study was to compare a population of patients with type 1 diabetes mellitus of more than 45 years’ duration and a control group for the prevalence of musculoskeletal disorders, pain, stiffness, and disability in the upper extremities and stiffness in the back.
1. In paper 1 we compared the prevalence of shoulder diagnoses, range of motion and self-reported shoulder disability in patients with long-term DM1 and controls and explored the association between long-term glycaemic burden and shoulder disability in the diabetes group.

2. In paper 2 we compared the prevalence of radiological glenohumeral OA according to the K-L classification in the two groups and explored the association between radiological OA and shoulder pain. In the diabetes group, we explored the association between the long-term glycaemic burden and OA.

3. We investigated the impact of different radiological classification systems on the prevalence of radiological and clinical glenohumeral OA in paper 3. The inter- and intra-observer reliability of the x-ray interpretation were reported.

4. In paper 4 we compared the prevalence of radiological hand OA, erosive hand OA and hand pain, disability and stiffness in long-term type 1 diabetes and controls. We also explored the association with the long-term glycaemic burden in the diabetes group.

5. The lifetime and point prevalence of Frozen shoulder, Carpal tunnel syndrome, Dupuytrens disease and Trigger finger as well as joint stiffness of the hand, shoulder and back in the groups were investigated in paper 5. We explored the association between stiffness and both collagen Advanced glycation end products and the glycaemic burden in the diabetes group as well.

3. METHODS

3.1 Participants and ethics

Patients

All patients who attended the Norwegian Diabetics Center (NDC) in Oslo, Norway in 2015 with DM1 since 1970 or earlier were eligible for the studies. Patients not able to cooperate with the clinical examination because of recent trauma or severe cerebrovascular disease were excluded.

Controls

We asked enrolled patients to bring their spouses or close friends to act as controls for the study. The controls were required to be free of diabetes as confirmed by a current HbA1c < 48 mmol/mol (6.5%). First-degree relatives were excluded.

Ethics

Written, informed consent was obtained from all subjects willing to take part in the study. The study received approval from the Regional Committee for Medical and Health Research Ethics South-East, Norway, project no. 2014/851.
3.2 Design

The study was an observational study with a cross-sectional, controlled design including patients with DM1 for more than 45 years and a control group without diabetes. We included all historical measurements of long-term glucose (i.e. HbA1c) for the diabetes patients and in this way the study also had a retrospective design.

3.3 Data collection

Descriptive data were collected at the Norwegian Diabetics Center via predefined questionnaires, interviews and medical records. At the Norwegian Diabetics Center skin biopsies and blood sampling were conducted. At Oslo University hospital, a standardised musculoskeletal-specific questionnaire was completed by the participants and a standardized clinical examination (appendix 1, 2) was conducted by one experienced medical doctor blinded for group affiliation. All participants underwent shoulder and hand x-rays (appendix 4), which were interpreted blinded for group affiliation.

We calculated a glycaemic index to describe the glycaemic burden in the diabetes patients over years (appendix 3). For the calculations, historical HbA1c data were collected from the patient files at the Norwegian Diabetics Center and when obtainable, from patient primary care files.

3.4 Outcome measures

A number of outcome measures were obtained for the analyses in the studies. They are listed in table 7 and described briefly in the third column in the table. For further descriptions of the variables and method used for the clinical and laboratory examinations, see the associated tables and appendices.
<table>
<thead>
<tr>
<th><strong>Outcome type</strong></th>
<th><strong>Outcome measure</strong></th>
<th><strong>Measure. Comment</strong></th>
<th><strong>Applied in paper no</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td>Age</td>
<td>Years</td>
<td>1-5</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>Male or female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td>Weight/height (m)^2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Waist circumference</td>
<td>Cm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Education</td>
<td>Dichotomized into low (upper secondary school) and high education level (college/university)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>Current smoker, past smoker, never smoked</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidity</td>
<td>Rheumatic disease, polyarthritis, psoriasis arthritis</td>
<td></td>
</tr>
<tr>
<td>Range of motion, shoulder</td>
<td>Active range of motion; flexion and external rotation</td>
<td>Degrees. See appendix 2</td>
<td>1, 2</td>
</tr>
<tr>
<td></td>
<td>Passive range of motion; external rotation and abduction</td>
<td>Degrees. See appendix 2</td>
<td></td>
</tr>
<tr>
<td>Shoulder, isometric muscle strength</td>
<td>External rotation and abduction</td>
<td>Newton. See appendix 2</td>
<td>1</td>
</tr>
<tr>
<td>Point prevalence</td>
<td>Shoulder diagnoses</td>
<td>% with diagnoses. See table 2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hand diagnoses</td>
<td>% with diagnoses. See table 6</td>
<td>5</td>
</tr>
<tr>
<td>Lifetime prevalence</td>
<td>Frozen shoulder</td>
<td>%. Point prevalence plus reported historical prevalence.</td>
<td>1</td>
</tr>
<tr>
<td>Duration frozen shoulder</td>
<td></td>
<td>Years. Reported duration for persons with frozen shoulder diagnosed at examination.</td>
<td>1</td>
</tr>
<tr>
<td>Hand stiffness</td>
<td>Prayer sign</td>
<td>Yes/no. Unable to reach full contact with palms and fingers when opposed.</td>
<td>5</td>
</tr>
<tr>
<td>Back stiffness</td>
<td>Fingertip-to-floor distance</td>
<td>Cm. Distance from fingertip to floor measured at maximum forward reach.</td>
<td>5</td>
</tr>
<tr>
<td>Shoulder pain</td>
<td>Worst pain last two weeks, NRS</td>
<td>3 or more on NRS from 0 to 10 for the question “How severe was your pain at the worst last week?”</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td></td>
<td>Pain during abduction, NRS</td>
<td>3 or more on NRS from 0 to 10 when doing maximal active abduction of the shoulder during the clinical examination.</td>
<td></td>
</tr>
<tr>
<td>Disability</td>
<td>Shoulder disability</td>
<td>Points. QuickDASH score (0 to 100).</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Hand disability</td>
<td>Points. AUSCAN score (0 to 60).</td>
<td>4</td>
</tr>
<tr>
<td>Glucose related measures</td>
<td>Current HbA1c</td>
<td>% Blood sample analysed in blood sample examination day. Normal value: 4.0-6.0% (20-42 mmol/mol).</td>
<td>1, 2, 4, 5</td>
</tr>
<tr>
<td></td>
<td>30 years HbA1c</td>
<td>Mean HbA1c value. See appendix 3.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estimated full duration HbA1c</td>
<td>Mean HbA1c value. Calculated value from start of the diabetes disease. See appendix 3.</td>
<td></td>
</tr>
<tr>
<td>Advanced glycation end products (AGEs)</td>
<td>From skin biopsy</td>
<td>Pmol/mg. Biopsy analysed for the following AGEs: Fructose-lysine, glucosepane, carboxymethyl-hydroxylysine (CML), carboxyethyl-hydroxy-lysine (CEL), pentosidine, MOLD, fluorophore LW-1, and methylglyoxal hydroimidazolone (MG-H1), and the oxidation product methionine sulfoxide (MetSOX).</td>
<td>5</td>
</tr>
<tr>
<td>X-rays</td>
<td>Shoulder x-ray</td>
<td>Standard x-rays after protocol. See appendix 4. Interpreted after 3 classification systems.</td>
<td>1, 2, 3</td>
</tr>
<tr>
<td></td>
<td>Hand x-ray</td>
<td>Standard x-rays after protocol. See appendix 4. Interpreted after the K-L classification system.</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 7. Demographic variables and outcome measures used in the studies.
3.5 Statistical methods

This study received statistical support for paper 1-3 and 5 from Oslo Center for Biostatistics and Epidemiology, Research Support Services. In paper 4 the analysis was done by the first author.

Based on the power analysis (type 1 error 5%, power of 90%) and an expected prevalence of shoulder and hand diagnoses of 36% in the diabetes group and 9% in the controls (21), 56 persons were needed in both groups to detect a significant difference in the prevalence of hand and shoulder diagnoses.

Table 8 gives an overview of the statistical methods used in the papers in this thesis.

We used the IBM SPSS version 23 for paper 1,2,4 and 5 and the STATA MP version 14 for paper 4.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Task</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Demographic data</td>
<td>Means (SD), medians (range) or proportions.</td>
</tr>
<tr>
<td>Paper 1</td>
<td>Differences between groups for linear variables.</td>
<td>Two-tailed Students t-test with mean difference, 95% confidence intervals and p-values.</td>
</tr>
<tr>
<td></td>
<td>Associations between categorical independent variables.</td>
<td>Chi-square or Fischer exact test for contingency tables.</td>
</tr>
<tr>
<td></td>
<td>Association between long-term HbA1c, QuickDASH score and shoulder range of motion.</td>
<td>Pearson correlation coefficients (r) with p-values.</td>
</tr>
<tr>
<td>Paper 2</td>
<td>Risk for having OA in the groups.</td>
<td>Pearsons Chi-square test presented as odds ratio with 95% confidence intervals and p-values. Logistic regression to control for gender, age, BMI, waist circumference and smoking.</td>
</tr>
<tr>
<td></td>
<td>Differences in groups with and without OA (within the DM1 group) for glycaemic burden.</td>
<td>Two-tailed Students t-test with mean difference, 95% confidence intervals and p-values.</td>
</tr>
<tr>
<td>Paper 3</td>
<td>Prevalence of OA</td>
<td>% of all.</td>
</tr>
<tr>
<td></td>
<td>Risk for having OA in the groups.</td>
<td>Pearsons Chi-square test presented as odds ratio with 95% confidence intervals and p-values.</td>
</tr>
<tr>
<td></td>
<td>Inter- and intra-tester reliability.</td>
<td>Weighted Cohens kappa with 95 % confidence intervals for ordinal variables.</td>
</tr>
<tr>
<td>Paper 4</td>
<td>Risk for having OA in the groups.</td>
<td>Pearsons Chi-square test presented as odds ratio with 95% confidence intervals and p-values.</td>
</tr>
<tr>
<td></td>
<td>Association between hand OA and glycaemic burden.</td>
<td>Regression analyses using the presence of long-term DM1, current HbA1c for cases and controls and the estimated full duration HbA1c (diabetes only) as continuous independent variables. Crude and adjusted</td>
</tr>
<tr>
<td>Paper 5</td>
<td>Difference in lifetime prevalence of hand and shoulder diagnoses between groups.</td>
<td>Two-tailed Students t-test or Mann Whitney U test for continuous and Pearson's Chi-square test for categorical variables. Presented as means or odds ratio with 95% confidence intervals and p-values.</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Stiffness explanatory data</td>
<td>Logistic regression with univariate, adjusted and multiple regressions with stepwise backward elimination for stiffness explanatory variables. Standardized values for advanced glycation end products (AGEs) and HbA1c variables were calculated for the regression analyses. We made a separate composite variable of AGEs that were significantly, or borderline significantly associated with stiffness in the adjusted model. In the adjusted model AGEs was adjusted for estimated full duration HbA1c. Variables with p&lt;0.20 in the univariate or adjusted (AGEs) analyses were included in the full model. The Benjamini-Hochberg procedure with a false discovery rate of 0.1 was used to adjust for multiple tests.</td>
</tr>
</tbody>
</table>

Table 8. An overview of the statistical methods used in the papers in this thesis.

4. STUDY RESULTS

Paper 1. Very high prevalence of frozen shoulder in patients with type 1 diabetes for more than 45 years. The Dialong shoulder study (1).

Objectives. To compare the prevalence of shoulder disorders and self-reported shoulder disability in patients with long-term type 1 diabetes mellitus and diabetes-free subjects; and to explore the association between the long-term glycaemic burden and shoulder disability in the diabetes group.

Design. Cross-sectional study of shoulder diagnoses with 30 years’ historical data on glycaemic burden in patients with diabetes.

Setting. Diabetics centre and a university hospital.

Participants. Subjects attending the Norwegian Diabetics Center in 2015 with type 1 diabetes since 1970 or earlier were eligible (n=136). One hundred and five patients were included, and 102 (50% women; mean age, 61.9 years) completed the study together with 73 diabetes-free subjects (55% women; mean age, 62.5 years).

Main Outcome Measure. Shoulder diagnoses decided through clinical examination according to scientific diagnostic criteria.

Results. Frozen shoulder was diagnosed in 60 (59%) patients with diabetes and 0 diabetes-free subjects, with a lifetime prevalence of 76% in the diabetes group versus 14% in the diabetes-free subjects. Patients with diabetes had higher disability and higher mean QuickDASH scores (23.0±19.9)
than diabetes-free subjects (8.9±12.0), with a mean difference of -14.2 (95% CI, -19.3 to -9.0) points (p<0.001). We found an association between chronic hyperglycaemia and QuickDASH scores, with a 6.16-point increase in QuickDASH scores per unit increase in HbA1c (p=0.014).

Conclusions. The point prevalence of frozen shoulder in patients with long-lasting type 1 diabetes was 59%, and the lifetime prevalence was 76%. The diabetes group had more shoulder disability than diabetes-free subjects. The historical HbA1c levels were associated with increased shoulder disability.

**Paper 2. The prevalence of radiological glenohumeral osteoarthritis in long-term type 1 diabetes.**

The Dialong shoulder study (2).

Objectives. This study compares the prevalence of radiological OA in patients with DM1 for more than 45 years and controls and explores the association with shoulder pain and glycaemic burden in patients with DM1.

Methods. The Dialong study is a cross-sectional, observational study with 30 years of historical data on long-term glycaemic control. We included 102 patients with DM1 and 73 diabetes-free controls. Demographic data, worst shoulder pain last week (numeric rating scale [NRS], 0–10), pain on abduction at examination (NRS 0–10), and current and historical HbA1c levels were collected. Standardized shoulder x-rays were taken and interpreted for OA applying the Kellgren–Lawrence classification.

Results. In the diabetes group (49% women), the mean (SD) duration of DM1 was 50.6 (4.8) years, mean 30-year HbA1c 7.4%, and age 61.9 (7.1) years. The mean age of controls (57% women) was 62.6 (7.0) years. Radiological gleno-humeral OA was found in 36 (35%) diabetes patients and 10 (14%) of the controls (OR 3.4 [95% CI 1.6 to 7.5]; p = 0.002). Few persons had moderate and severe OA (6.9% vs 1.3%, OR 5.3 [95% CI 0.6 to 44.1]; p = 0.1). Fifteen of the diabetes patients had painful OA versus two controls (adjusted OR 5.4 [95% CI 0.6 to 47.9]; p = 0.13). There was no association between OA and long-term glycaemic burden (mean 30-year HbA1c) in the diabetes group (p > 0.2).

Conclusions. Radiological gleno-humeral OA was more common in patients with DM1 than in controls for mild, but not moderate and severe OA. The radiological findings were not associated with shoulder pain or long-term glycaemic burden.

**Paper 3. Reliability and prevalence of radiological glenohumeral osteoarthritis in long term type 1 diabetes using three classification systems.** The Dialong shoulder study.

Submitted to Skeletal Radiology, December 8th, 2017.
Objective. Shoulder pain affects one third of persons with long-lasting type 1 diabetes mellitus (DM1). The association between DM1 and glenohumeral osteoarthritis (OA) has not been studied. In the present study, we evaluate the intra- and inter-rater agreement of radiological glenohumeral OA using three different classification systems and estimate the prevalence of radiological and clinical glenohumeral OA in long term DM1 and controls.

Subjects and methods. We included 102 patients with DM1 duration > 45 years (49% women, mean age 61.9 years) and 73 diabetes free controls (57% women, mean age 62.6 years). Standardized shoulder x-rays were interpreted by two observers for OA applying the Kellgren-Lawrence, Samilson-Prieto, and Samilson-Prieto Allain classifications.

Results. The inter-rater agreement was moderate for all classifications (weighted kappa 0.46 to 0.48). The agreed prevalence of total radiological OA was 26 to 44% in the diabetes group and 17 to 26% in controls depending on classification system. The prevalence of moderate or severe radiological OA was 1 to 6% and clinical OA 1 to 2%. Neither differed between the groups.

Conclusion. Inter-rater agreement was moderate for all three classification systems and the prevalence of radiological glenohumeral OA varied between the classification systems. These factors should be considered in the reporting of radiological glenohumeral OA. The prevalence was higher in the diabetes group with two of three classification systems but not associated with clinical glenohumeral OA. Moderate and severe radiological and clinical glenohumeral OA were rare, not different between the groups and comparable to the general population.

Paper 4. Long-term type 1 diabetes is associated with hand pain, disability and stiffness, but not with structural hand osteoarthritis features. The Dialong hand study (3).

Objective. To explore whether having long-term type 1 diabetes (>45 years) is associated with a higher prevalence of radiological hand OA, erosive hand OA and increased hand pain, disability and stiffness.

Methods. In total, 96 persons with type 1 diabetes diagnosed before 1970 were included (mean [SD] age: 62.2 [7.4] years, mean [SD] HbA1c: 7.43 [0.80], 49 [51%] men). Regular measurements of their HbA1c were obtained till 2015. We included 69 healthy controls without any diabetes (mean [SD] age: 63.0 [7.0] years, mean [SD] HbA1c: 5.41 [0.32], 29 [42%] men). The groups were compared for radiological hand OA (Kellgren-Lawrence grade ≥2 in ≥1 joint) and erosive hand OA (central erosions in ≥1 joint), Australian/Canadian index (AUSCAN) for hand pain, disability and stiffness using regression analyses adjusted for age, sex, educational level and waist circumference.
Results. We found no associations between having long-term type 1 diabetes and more prevalent radiological hand OA (OR = 1.11, 95% CI = 0.55 to 2.26). We found a trend towards higher prevalence of erosive hand OA in diabetes patients (OR = 2.96, 95% CI = 0.82 to 10.64). Strong and consistent associations were observed between long-term type 1 diabetes and increased hand pain (β = 2.78, 95% CI = 1.65 to 3.91), disability (β = 5.30, 95% CI = 3.48 to 7.12) and stiffness (β = 2.00, 95% CI = 1.33 to 2.67). These associations were particularly strong for women and participants below the median age of 61 years.

Conclusion. Long-term type 1 diabetes was not associated with radiological hand OA, but was strongly associated with hand pain, disability and stiffness. The association between diabetes and erosive hand OA warrants further investigation.


Aims: We aimed to: estimate the prevalence of Dupuytrens disease, trigger finger, carpal tunnel syndrome and frozen shoulder; assess stiffness of the hand, shoulder and back; and explore the association of joint stiffness with both long-term HbA1c and collagen advanced glycation end-products (AGEs) in long-term type 1 diabetes mellitus (DM1).

Methods: Patients with DM1 from 1970 or earlier attending a specialized diabetes centre were included in this cross-sectional controlled study. We collected HbA1c measurements from 1980 to 2015 and data on hand and shoulder diagnoses and joint stiffness through interviews, charts, and standardised examination. Skin biopsies were analysed for collagen AGEs by liquid chromatography-mass spectrometry.

Results: Lifetime prevalence of hand and shoulder diagnoses in the diabetes group (n = 102) ranged from 37% to 76% (frozen shoulder) versus 11% to 15% in controls (n = 73) (p < 0.001). There was an association between joint stiffness and long-term HbA1c (odds ratio 2.01 [95% CI 1.10 to 3.7]) and the AGEs methyl-glyoxal-lysine-dimer (odds ratio 1.68 [95% CI 1.03 to 2.73]) and pentosidine (odds ratio 1.81 [95% CI 1.04 to 3.16]).

Conclusions: Patients with DM1 > 45 years had a very high prevalence of hand and shoulder diagnoses versus controls. Joint stiffness was associated with collagen AGEs. However, joint biopsies and prospective studies must explore this association further.
5. GENERAL DISCUSSION

5.1 Study design

We chose an observational cross-sectional design and included patients who had been exposed to DM1 for 45 years or more. We also included a diabetes free control group to compare our findings. There are a number of advantages and disadvantages with such a design (127).

Advantages:

- You may study rare conditions because the diseased individuals are already identified.
- The study can be deducted in less time because the disease has already occurred and been present for a very long-time period.
- If chronic hyperglycaemia is associated with the outcomes the long exposure of hyperglycaemia in the exposed group would make it possible to detect or exclude such an association.

Disadvantages:

- There is no randomization and imbalance of characteristics in patients and controls may include confounding factors affecting outcome.
- The diabetes group consists of the survivors of the disease after > 45 years. The association between chronic hyperglycaemia and the outcomes might differ in the diseased group not studied or the dead.
- The design is partly retrospective, and information rely on the subjects’ memory which give the possibility of recall bias.
- Blinding during examination may be difficult due to characteristics of the diseased individuals like the increased prevalence of contractures of the hands or the use of glucose measurement devices and insulin pumps.

We were able to establish a cohort of patients because most patients at the Norwegian Diabetics Center (NDC) have been followed up there from the debut of their disease. The patients of interest should have had a very long exposure to DM1 and we chose a cut off of at least 45 years to include a sufficient number of patients to have acceptable statistical power in the analysis. Most patients had medical charts for the entire disease period with listing of diabetic complications, comorbidities and long-term glucose values (HbA1c) for more than 40 years in most of the patients. This made it possible to estimate the exposure to hyperglycaemia quite accurately over a very long-time period.

Because of the retrospective design we were not able to do a randomisation procedure and had to establish a control group at the time of examination. To be able to evaluate the effect of exposure we included a diabetes-free control group. The most suitable controls should preferably be matched for characteristics of importance for the observed outcomes (127). Our control group consisted of
spouses and friends gathered without matching. Anyway, the groups turned out to be quite similar regarding demographical variables.

5.2 Reporting of the studies

The Equator network was established in 2006 with the purpose of enhancing the quality and transparency of health research (EQUATOR) (128). Their web-page comprises guidelines for the reporting of many study types including observational and diagnostic studies (129).

Reporting of observational studies have been criticised for insufficient quality that makes it difficult to assess the strengths and weaknesses of the studies and their generalisability (130). The Strengthening the reporting of observational studies in epidemiology (STROBE) initiative promotes recommendations to improve the quality of reporting and provide checklists for the use with reporting (131). We have reported our results in accordance with the STROBE initiative.

5.3 Internal validity

Internal validity is the degree to which the results of a study are correct for the sample of patients being studied. A number of factors may influence the internal validity (127, 132).

5.3.1 Measurement or detection bias

Measurement bias is a threat to the internal validity and should be considered carefully. In this study, a lot of measurements were done, both patient-reported, clinical examinations executed by an examiner as well as laboratory tests and imaging.

Demographical variables are considered quite stable and not very exposed to bias. This is true for age, gender and duration of diabetes and also for the simple measurements of weight, BMI and waist circumference. Smoking habits and education level are more likely to be affected by recall bias. We did not check the validity of these variables. For comorbidity a combination of interview and chart review was used, and the validity of the information from the interviews was checked for in the Norwegian Diabetics Centers archives.

Musculoskeletal outcomes measures consisted of examiner conducted measurements of range of motion, strength and stiffness, clinical tests and radiological examinations of the shoulders and hands. All clinical tests were chosen in accordance with the diagnostic criteria reported for the expected diagnoses in shoulder and hands as well as stiffness in the shoulders, hands, neck and low back. The test procedures were predefined and standardised to minimize measurement bias. The same examiner performed the clinical examinations after a predefined protocol and in a
standardised sequence for all research subjects. Using only one assessor may increase the possibility for systematic errors, but would abolish the inter-observer variability. We did not assess the intra- or inter-tester reliability for the musculoskeletal outcomes which reduces the confidence in the results.

**Shoulder range of motion (ROM)** was measured both as passive and active movements in different directions with respect to the importance of the movements for the patients in daily life and for the evaluation of shoulder stiffness and shoulder diagnoses. We used a manual goniometer to measure active flexion and external rotation. The inter-tester reliability is earlier found to be fair to good (42) or excellent (64) with excellent intra-rater reliability with 12° and 13° estimated minimal detectable change (65). To estimate passive external rotation and passive abduction we used visual estimation which earlier is questioned as an outcome measure (63). However, the method has also demonstrated fair to good inter- and intra-tester reliability (42). The hand behind back measurement have showed poor intra-tester reliability (42). Even though some of these measurement methods show acceptable measurement properties small differences should be interpreted with care.

**Shoulder muscle strength** was assessed in a standardised fashion. Still motivation and the habit of producing maximal force varies in people and may affect the test results (133). Shoulder pain is known to interfere with force production in the shoulder (134). The tests in our study were done standing which is a little more demanding than sitting. This could in particular disturb persons with balance problems not being able to exert maximal force when tested. Anyway, the strength testing was done with the main aim of detecting large loss of muscle force compatible with full thickness tears of the rotator cuff. For this purpose, the effect of the biases of measuring strength discussed here should be small and not devastating.

**Stiffness.** The measurements of the occiput-to-wall-distance (OWD) was zero cm for all participants except for two persons with severe kyphoscoliosis of the thorax. We realized that OWD was not a suitable measure for neck stiffness because of the ceiling effect and did not find the examination valid in our setting. The results are not published.

Stiffness in the shoulder was based on a reduced passive external rotation outside 2 SD from normative values in pain free subjects supplemented with correspondingly one of reduced abduction or flexion. This means that if we presume that the normal values are correct a reduction in range of motion of more than 2 SD is found in only 2.5% of a population. To be labelled as stiff in our study the range of motion had to be outside 2 SD in passive external rotation and one of passive abduction or active flexion. Such stiffness represents a significantly reduced ability to move the shoulder and we considered it as a robust measure of shoulder stiffness. Numerous studies have defined frozen
shoulder as having reduced range of motion (56-58, 60, 61). Most of the studies requires a reduction of 30° or more which we adapted. However, the defined stiffness is not a validated diagnostic measure for frozen shoulder. Thirty degrees is well outside the estimated minimal detectable change for external rotation (65) and should represent a confident measure of stiffness.

Stiffness in the hand was decided to be present with a positive prayer sign without the coexistence of widespread Dupuytren's disease. When the prayer sign is positive, movement of all or most of the metacarpal and interphalangeal joints in the hand are affected by tightness in the periarticular connective tissue and the changes are severe enough to manifest as flexion contractures of the joints. This condition is almost never found in persons without diabetes and is a quite confident measure of diabetic stiffness in the hand when present (79). There is a lack of reliability studies for this test.

Stiffness in the back was measured indirectly as the subjects’ ability to lean forwards with straight legs to touch the floor. The Fingertip-to-floor distance was measured in cm. The test has shown excellent inter-tester reliability but with a relatively large minimal detectable change of 9.8 cm (114, 135). In the present study, 42% of the diabetes group reached the floor vs 51% in the control group. The subjects did not stand on a raised platform and therefore we were not able to record negative values for a better range. Shortcomings in the Fingertip-to-floor distance may be caused by stiff hip joints, short hamstrings muscles, long legs relative to arm length as well as abdominal adiposity and back stiffness. Stiffness in the back might be due to stiff connective tissue in the vertebral column, but also caused by shortened back muscles. Fingertip-to-floor distance may be considered as a surrogate measure for stiffness of the collagen fibres in the connective tissue in the back and the measurements are tampered with uncertainty.

5.3.2 Musculoskeletal diagnoses and diagnostic criteria

Most atraumatic diagnoses in both the shoulder and the hand are made on the basis of a clinical examination alone and there are no objective reference standards to compare to except for OA and full thickness rotator cuff tears which require both pain or loss of function along with corresponding pathology on imaging (26). Paper 1, 2 and 5 concerns clinical diagnoses. All diagnoses were set as present or absent whether the diagnostic criteria were met or not. In some cases, the diagnostic triage was somewhat uncertain because of doubtful results from the examination. Even though most of the examinations needed for the diagnostic triage are quite easy to perform, the reported intrarater reliability in studies varies (table 3) (136) and systematic reviews of the performance of physical examination tests show poor test properties (46, 137). Together this implies a risk of detection bias
for the diagnoses which may have both increased and decreased the reported prevalence in the study.

5.3.3 Radiological outcomes

Radiological outcomes consisted of plain x-rays of both hands and both shoulders taken in one laboratory. An effort was done to standardise the imaging procedures and thereby minimize measurement bias. The protocol was predefined (appendix 4), and the procedures were conducted in one laboratory by the same team of technicians with a professional bachelor degree in radiography. The interpretation of the films was done after predefined classification systems by experienced musculoskeletal radiologists, both with over 20 years of experience in the field to minimize variation. Reliability testing of the interpretation was done using weighted Cohens kappa statistics to calculate the degree of agreement between and within the observers. Cohens kappa was introduced instead of percent agreement to control for chance (138). Cohens kappa measures reliability and is a relative measure of agreement in contrast to proportions of specific agreements. This fact is debated and Cohens kappa may give very low kappa values in certain circumstances (139). The weighted Cohens kappa is suitable for ordinal variables with ranked categories like the radiological OA classifications. In paper 2 and 3 the importance of having two independent observers interpreting the films was highlighted by the impact on the prevalence of radiological glenohumeral OA. The use of kappa statistics for the measures of reliability clearly showed the uncertainty of interpreting the milder degrees of radiological glenohumeral OA which had important implications on the conclusions in paper 3.

5.3.4 Patient reported outcome measures

Patient reported outcome measures include shoulder pain and scores of disabilities of the shoulders and hands. Pain was measured with a Numeric rating scale which is a widely used and an accepted way to measure pain (119). QuickDASH and AUSCAN are region-specific scores used for evaluation of disability in the shoulder and hand. Both are translated to Norwegian and validated in Norwegian populations and normative values exist for comparison. Scores achieved with these scales are considered valid for evaluation of shoulder and hand pain and disability in recent systematic reviews (140, 141). However, more and better studies on the measurement properties of DASH/QuickDASH is warranted (141).

5.3.5 Historical prevalence of shoulder and hand diagnoses

The historical prevalence was determined through questionnaires at two different time points and in an interview as well. The two questionnaires were checked against each other to give the best
possible data. The variation between the questionnaires was small but the crude numbers are not reported here. For the diabetes group, the files at the Norwegian Diabetics Center were checked for the diagnoses. Even if a considerable effort was done to ensure the quality of these data the possibility of recall bias must be considered.

5.3.6 Glucose-related outcomes

Glucose-related outcomes were both current and historical. Current values were obtained through blood samples analysed for current HbA1c. The analyses were all done in an accredited hospital laboratory and therefore the obtained values must be considered representative with minimal measurement bias. For the long-term values, most measurements were collected from the patient files at the Norwegian Diabetics Center. The measurements were done in the Norwegian Diabetics Centers laboratory assuring little measurement bias. For the glycaemic burden we did two different calculations (appendix 3). The method for calculating 30-year HbA1c is used earlier in the large DCCT/EDIC studies and reckoned as a valid measure for glycaemic burden (142). To get a measure that might reflect the disease-long glycaemic burden better we calculated a new measure: Estimated full duration HbA1c. This method is not used earlier and not validated against other measures of diabetes disease. The possibility of measurement bias is accordingly larger for this method.

5.3.7 Blinding

Both the clinical assessment and obtaining and interpretation of the x-rays of the shoulders and hands was done by assessors blinded for group affiliation to avoid observer bias. Some of the patients with diabetes wore equipment for measurement of blood glucose and some had insulin pumps attached to their bodies. Even if most research objects wore t-shirts at examination it was impossible not to notice the equipment and the blinding was obscured for some persons in the diabetes group. The research nurse urged all participants not to tell whether they had diabetes or not, but some told it anyway. This could have influenced the examination, making the investigator more prone to notice pathology and thereby increase the difference to the control group. It was impossible to reveal group belonging at imaging and for the radiologists who interpreted the x-rays.

5.3.8 Confounding bias

Confounding bias is always a concern in research and especially in observational studies. Controlling for known prognostic factors may reduce this problem, but it is always possible that a forgotten or unknown factor was not included or that factors interact complexly. Confounding has been described as the most important limitation of observational studies (127). In the present study, we have controlled for known confounders like age, sex, education level, smoking, waist circumference and
BMI in the regression analyses. There were no significant differences between the groups for the demographical data.

5.3.9 Summary of internal validity

We consider the internal validity of our study as acceptable, but realize the possible variation in prevalence with the evaluated elements. The selection of participants may be considered robust. The demographic data were comparable between the groups even if the controls were few. On the other hand, for most of the clinical tests and the diagnoses, the likelihood of detection bias was considerable even though we strived for standardisation through predefined and systematic procedures, using only one examiner, blinding to the possible extent and doublechecking of variables vulnerable for recall bias.

5.4 External validity

External validity is the degree to which the results of a study holds true in other settings or may be generalised to other populations (127). A number of factors may affect the external validity (132, 143).

5.4.1 Selection bias or choice of research objects

All patients attending the Norwegian Diabetics Center in 2015 diagnosed in 1970 or earlier with DM1 (n=136) were invited to the study. DM1 was defined as a history typical of DM1, HbA1c > 6.5% (48 mmol/mol) and lack of insulin production as evidenced by a fasting c-peptide concentration < 0.2pmol/ml. Most of the patients had attended the Norwegian Diabetics Center for more than 30 years. One hundred and five patients accepted the invitation and 102 fulfilled all tasks in the study. We were not allowed to use information from the patient charts for the 34 patients fulfilling the inclusion criteria not taking part in the study. However, for age, gender and duration of diabetes they did not deviate from the included cohort.

The controls (n=73) were recruited through the patients and not through matching of specific criteria which allowed for bias in the demographic variables. In general, gender, age, body mass index, smoking, education level and comorbidity are associated with pain, disability and stiffness in the musculoskeletal system (133). Emotional distress as anxiety and depression may also affect the individuals pain experience and expression of disability (134). We assumed that spouses and close friends would inhabit similar characteristics as the diabetes patients. The two groups in the study did not differ significantly with regards to any of the demographics variables (age, gender, body mass index, waist circumference, smoking, education level or rheumatic comorbidity). We recruited less
controls than diabetes patients which may be considered a weakness. However, sample size calculations showed that the group sizes were sufficient and the similarity in demographic data between the groups strengthens the internal validity.

One of the properties of the studied diabetes population were well defined, they all suffered from DM1 and had all been diseased 45 years or more. The mean current HbA1c value in our population was 7.4% while the mean HbA1c in 2015 in the Norwegian Diabetes Register for patients with diabetes duration of 45 years or more was 7.6%. The mean HbA1c values did not differ significantly from each other (p=0.078) which increases the trust in the transferability of our results to other patients who have suffered from DM1 45 years or more. On the other hand, we do not know whether the patients attending the Norwegian Diabetics Center are representative for patients in other regions of Norway receiving care in primary care or specialist centres organized differently. Such circumstances may contribute to difference in patient characteristics and reduce the external validity of this study (143).

Most patients with DM1 are diagnosed in adolescence and have lived with the disease for 10, 20, 30 years or more. Our population did not include patients with DM1 for less than 45 years and consequently the transferability of our results to these groups is more uncertain. However, we found significant and strong associations between the long-term HbA1c and hand disability, shoulder disability and having phase one or two painful shoulders. These findings could be interpreted as if the risk of such complications increases with the long-term HbA1c and encourage all patients with DM1 to keep their blood glucose as low as feasible. In this respect, our results are transferable to all patients with DM1.

The choice of outcomes was mainly based on clinical relevance for DM1 patients and in primary care. All clinical examinations were chosen to cover the most prevalent clinical diagnoses in the shoulder and hand reported both in primary care in general and in diabetic populations and were easy to perform with acceptable reliability (26). The Patient reported outcome measures (QuickDASH and AUSCAN) were both translated to Norwegian and validated in a Norwegian population earlier (121, 125). Normative values for different age-groups were available for QuickDASH (120) and the results of this study were easy to compare to the normative values. Plain x-rays were taken for evaluation of OA. All these choices were done to increase the generalisability of our results beyond specialist care or tertiary care as represented by the Norwegian Diabetics Center.
5.5 Statistical approach

Sample size estimations are used to determine how many subjects are needed to answer the research question (127). The Dialong study was planned to explore complications in multiple organ systems in very long DM1. The power analysis was based on the relationship between coronary artery disease on computer tomographic coronary angiography and levels of the AGE Glucosepane in skin in diabetic patients. Seventy-seven diabetes patients were a robust estimate with 90% power to discover a significant difference in skin Glucosepane levels between patients with type 1 diabetes with normal coronary arteries versus obstructive coronary artery disease. The study aimed at including 100 patients with DM1.

The prevalence of typical clinical disorders in the shoulders and hands in diabetes (cheiroarthropathy) was earlier reported to be 36% in patients with DM1 and 9% in control patients (22). With a true probability of exposure in cases of 36%, we would need to include 56 patients in each group, a total of 112 subjects, considering a type I error of 5% and a power of 90%.

We did not do separate sample size calculations for the studies on prevalence of OA in the hands and shoulders and had no possibility to increase the power for these studies.

The present study included 102 patients with DM1 and 73 controls which much be considered sufficient for detecting true group differences in clinical diagnoses (paper 1 and 5), but too small to detect true differences in rare diagnoses as radiological erosive hand OA (paper 4) and moderate to severe radiological glenohumeral OA (paper 2 and 3).

In paper 3 and 4 we investigated the reliability of interpreting x-rays of the shoulder and hand. Reliability concerns the degree to which repeated measurements provide similar answers (144). In paper 3 we evaluated radiological glenohumeral OA with three different classification systems, all of which divides OA into four or five grades. For ordinal measures the weighted Cohen’s Kappa coefficient is recommended (144) and was applied to estimate both inter- and intra-tester reliability. It is recommended to evaluate a sample size of at least 50 for the calculations (144). We used all images (350 shoulders) for the inter-tester calculations. A re-interpretation was done by both observers 2-3 weeks after the initial interpretation for 120 randomly chosen images to calculate the intra-tester reliability. The samples were both inside the recommended size. The results showed moderate weighted kappa values (0.46-0.47) which is somewhat lower than 0.70 which is recommended as the minimal standard for reliability (144). In paper 4 the prevalence of hand OA was calculated. Because of the multiple joints in the hand a sum score (0 to 120) based on the K-L scores in all the individual joints was made. Twenty randomly chosen films were re-evaluated after
several weeks to estimate the intra-rater reliability. The Intraclass Correlation Coefficient (ICC) was used because the K-L sum score was a continuous measure (144). The ICC scores for intra-tester reliability were excellent (0.95-1.00), but the sample size used for re-interpretation smaller than recommended. The inter-rater reliability was not calculated which also weakens the results of this study somewhat.

To calculate group differences, we used Students t-tests for the continuous variables in paper 1 and Chi-square tests presented as OR with confidence intervals to detect differences between categorical independent variables in paper 1, 2 and 3. The diabetes group and the control group represent individual samples, but the demographical variables were without statistical difference which make the choice of methods appropriate.

For associations between long-term HbA1c and other variables in paper 1, 2, 4 and 5 we used linear and logistic regression analyses adjusted for general covariates as age, gender, smoking, waist circumference and BMI.

5.6 Main results compared to current evidence

5.6.1 Frozen shoulder and shoulder disability

In paper 1 we found the point prevalence of frozen shoulder in the diabetes group to be 59% with a lifetime prevalence of 76%. This is the highest reported prevalence in the literature for patients with DM1. Earlier studies have included patients with shorter disease duration, but with comparable HbA1c. All studies report lifetime prevalence (table 9).

<table>
<thead>
<tr>
<th>Study, year of publication (ref.)</th>
<th>Mean age (SD)</th>
<th>Duration of disease, years (SD)</th>
<th>Frozen shoulder (%)</th>
<th>HbA1c, % (SD)</th>
<th>Mean 30-years HbA1c, % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arkkila, 1996 (22)</td>
<td>33 (10)</td>
<td>18 (10)</td>
<td>10</td>
<td>7.9 (1.5)</td>
<td></td>
</tr>
<tr>
<td>Caglierio, 2002 (21)</td>
<td>40 (11)</td>
<td>22 (11)</td>
<td>16</td>
<td>8.0 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Larkin, 2014 (20)</td>
<td>52 (7)</td>
<td>31 (5)</td>
<td>31</td>
<td>8.0 (1.0)</td>
<td>8.0 (1.0)</td>
</tr>
<tr>
<td>Juel, 2017 (1)</td>
<td>63 (7)</td>
<td>51 (5)</td>
<td>76</td>
<td>7.4 (0.8)</td>
<td>7.7 (0.8)</td>
</tr>
<tr>
<td>Juel, point prevalence</td>
<td>63 (7)</td>
<td>51 (5)</td>
<td>59</td>
<td>7.4 (0.8)</td>
<td></td>
</tr>
</tbody>
</table>

Table 9. The lifetime prevalence of frozen shoulder in studies on DM1.

All studies found an association with age and disease duration except ours. Most likely this is due to the selection of our cohort that was based on a diabetes duration >45 years with a resulting interquartile range of only 7 years. This makes it difficult to draw a conclusion about the association
between disease duration and shoulder diagnoses. Anyway, there is a striking increase in the lifetime prevalence of frozen shoulder with disease duration across the studies (figure 5).

![Graph showing the prevalence of frozen shoulder (FS) according to duration of type 1 diabetes in 4 cohorts.](image)

Figure 5. Lifetime prevalence (%) of frozen shoulder in four cohorts of subjects with increasing disease duration. Arkkila (22), Cagliero (21), Larkin (20), Juel (1).

The diagnostic criteria for frozen shoulder vary among the studies. Larkin et al. (20) did not specify any pre-set criteria but included a question (“Have you ever been told that you have “frozen shoulder” or adhesive capsulitis?”) and included other upper limb questions as well without explaining the use of these. Cagliero et al. (21) considered frozen shoulder to be present when “unilateral shoulder pain had been present for over 3 months and the range of external rotation and active and passive shoulder movements in all planes was less than 50% of normal.” A history of prior surgery for the disorder was also considered as evidence. Arkkila et al. (22) used “shoulder pain for at least one month, an inability to lie on the affected shoulder, and restricted active and passive shoulder joint movements in at least three planes” as criteria for frozen shoulder or written documentation of having had these symptoms and signs in the past. Obviously, there is room for interpretation in the above-mentioned criteria and all studies includes historical confirmation of the diagnosis which make them vulnerable to recall bias. In our study, we tried to be as transparent as possible in the diagnostic process and reduce bias as much as possible. Using such methods, the point prevalence alone was much higher in our study than the reported prevalence in the other studies indicating strongly an increase of shoulder stiffness with disease duration. Taking lifetime prevalence into account this indication becomes even stronger (figure 5).
When patients in general are diagnosed with frozen shoulder their shoulder is painful. The natural course of the disease described in the introduction (1.2.3) involves increasing stiffness and gradually reduction of the pain. After some months, the stiffness dissolves as well in most cases (59, 60). In our population, this process seems to have shifted because 68% of the patients classified with frozen shoulder had stiff, not painful shoulders. Fifty percent of these were affected bilaterally. The mean duration of frozen shoulder was 13.6 years which is approximately 12 years longer than reported in diabetes free persons (60). No other studies have reported stiffness without pain, bilateral occurrence or prolonged duration. It is tempting to link the overt stiffness and the prolonged course to the load of having diabetes for 50 years. For the diabetes-related variables we found an association between having frozen shoulder and both 30-year HbA1c and estimated full-duration HbA1c. This is in accordance with earlier reports (20-22). We found no associations between the Advanced glycation end products measured in skin biopsies and frozen shoulder as reported in paper 5, but suggests that biopsies from the shoulder capsule and not the skin, could better reflect whether such an association exists.

Corresponding to the high prevalence of frozen shoulder we found significant reduced range of motion in the diabetes group for all measurements. No other studies have reported comparable values.

The diabetes group reported significant higher shoulder disability than controls with the QuickDASH questionnaire (SD); 23 (20) vs 9 (12) points. Subjects with painful frozen shoulder (phase 1-2) scored higher; 40 (16) points and in particular women with painful frozen shoulder; 46 (13) points. In the mentioned studies above on DM1 only Larkin et al. (20) reported disability with a mean QuickDASH score (SD) ranging from 6 (10) to 16 (16) points dependent on grouping for the number of diagnoses in the hand and shoulder (0, 1 or 2 diagnoses). They did not report separately for women or subjects with frozen shoulder. These values are well lower than the normative QuickDASH (SD) scores reported in comparable Norwegian age groups (40-49) for women; 14 (19) and men; 10 (17) (120). The reason for this huge difference in reported disability between Larkin et al. and our cohort is difficult to explain in full, but may indicate that pain and gender as well as disease duration are important factors for disability.

5.6.2 Glenohumeral osteoarthritis

In paper 2 and 3 we reported the prevalence of radiological glenohumeral OA in the cohort and in paper 3 we investigated the reliability of three different scoring systems.
5.6.2.1 The reliability of radiological interpretation of glenohumeral osteoarthritis

In paper 3 two experienced radiologists interpreted all images independently and blinded for group affiliation using three different classification systems; the Kellgren-Lawrence, the Samilson-Prieto and the Samilson-Prieto Allain classifications. The inter-rater reliability was only moderate for all classifications which was somewhat surprising with two very experienced observers who also went through an agreement session for interpretation of the classifications prior to the study. The inter- and intra-rater agreement of the classifications have been investigated earlier and are reported to be moderate to almost perfect (96, 98, 104). One study found that both inter- and intra-rater agreement of the Samilson-Prieto classification varied with different degrees of external and internal rotation in the shoulder during imaging (105) and the intra-rater agreement is also shown to vary in different populations (98, 104). In asymptomatic populations some degeneration is found to be common in the knee and the spine (145, 146), but this has not been evaluated in the shoulder.

The Kellgren-Lawrence classification was developed to evaluate knee and hip OA and has been criticised as inappropriate for the non-weight-bearing glenohumeral joint due to the difficulty in classifying the minor joint space narrowing required for grade 2 OA (98, 104). No exact measure for the assessment of the narrowing is given and the evaluation is thus subjective. An age-related joint space narrowing is also reported (100), which hampers the evaluation of the joint space further in older populations. The Samilson-Prieto classifications depend on the existence and size of osteophytes. Small osteophytes may be difficult to recognize and differentiate due to the possible variations in the angle of the x-ray tube even with strict image standardization as in the present study (147). Zero to 20 degrees external rotation of the glenohumeral joint during imaging is shown to reduce intertester agreement considerably which also increases the likelihood for misinterpretation of small osteophytes (105). Our findings of lower inter-tester agreement in the diabetes group which had significantly less external shoulder rotation than the control group (1) is in keeping with this.

The intra-rater agreement was substantial (0.63-0.81) for both observers and all classifications. This is in line with an earlier report from a general population (96).

Both the inter- and intra-rater agreement in the present study was lower than in a surgical population (98) which may reflect better inter-rater agreement in populations with more severe radiological OA.

5.6.2.2 The prevalence of radiological glenohumeral osteoarthritis

In paper 2 we estimated a prevalence 36% of radiological glenohumeral OA in the diabetes group versus 14% in the control group using one observer. In paper 3 we also report a higher prevalence of radiological glenohumeral OA in the diabetes group using the osteophyte based Samilson-Prieto and
the Samilson-Prieto Allain classifications, but not with the Kellgren-Lawrence classification. The 36% and 14% prevalence of radiological glenohumeral OA reported in paper 2 with the Kellgren-Lawrence classification differed from the 26% and 18% in the diabetes and control groups respectively reported with the same classification system in paper 3. The difference in prevalence is most likely due to the agreed prevalence obtained with two observers in paper 3. The inter-rater agreement obtained for the Kellgren-Lawrence classification was moderate and the results underlines the pitfalls of using one observer only. A 5% prevalence of radiological OA is reported in a community dwelling Korean population with the K-L classification (92). They used one observer and did not report the imaging procedure.

For the Samilson-Prieto classification, the observed 26% prevalence in the control group in the present study is higher than the 16% and 17% prevalence reported in previous studies in the general population (96, 97). Both studies used observations from one observer only giving room for systematic interpretation errors. Furthermore, the lower prevalence compared to our study may be brought about by several factors such as: ethnicity, differences in workload and age (105, 147), as well as selection bias due to the relatively small sample size in the present study (148).

The prevalence of radiological OA with the Samilson-Prieto Allain classification was lower than with the Samilson-Prieto classification in the present population for both the diabetes and the control groups. The prevalence may have been influenced by the stricter criteria for the separation between grade 0 and 1 with the Samilson-Prieto Allain classification requiring at least a 1 mm osteophyte to achieve grade 1 OA (105, 147). We found no comparable studies using the Samilson-Prieto Allain classification.

The prevalence of moderate and severe radiological OA was low in both the diabetes and control group for all classifications, still the prevalence varied from 2 to 5 percent in DM1 and from 1 to 6 percent in controls depending on the classification system applied. The 4 to 6% prevalence observed with the Samilson-Prieto and Samilson-Prieto Allain classifications are comparable to the prevalence reported in a Japanese population (96).

Clinical glenohumeral OA was diagnosed in shoulders with both pain and radiological glenohumeral OA, but without frozen shoulder, in 5 to 7% of the persons in the complete cohort. There was no significant difference between the diabetes and control group. To our knowledge, no comparable studies reporting clinical OA in the glenohumeral joint are available.
5.6.3 The prevalence of radiological hand osteoarthritis and disability

Paper 4 reported the prevalence of OA and disability in the hands. We found no difference in radiological OA between the patients with DM1 and the controls. Hand OA in diabetes is scarcely reported in the literature. A SR and meta-analyses (mainly type 2 diabetes) from 2015 contains only two reports on hand OA and diabetes. The report indicated a higher prevalence of diabetes mellitus in persons with hand OA than in persons without (107), but not higher prevalence of OA in persons with diabetes than diabetes-free persons. A later study of hand OA and type 2 diabetes showed no such association (109). In our study, only patients with DM1 lasting 45 years or more was included. This represents a very long disease duration with a pathological glycaemic burden on the joints over many years. The failure to show increased hand OA compared with a control group strengthens the hypothesis that there is no association between diabetes and hand OA.

Contrarily, hand disability measured with AUSCAN was increased in the diabetes group. The increased disability could not be explained by radiological hand OA and was significantly associated with long-term HbA1c even after adjustment for the increased prevalence of Carpal tunnel syndrome, Trigger finger, Dupuytrens disease and Limited joint mobility of the hand which previously have been shown to be increased in persons with diabetes (19, 20, 23). The reason for the strong association between DM1 and the AUSCAN variables is difficult to explain from the present material and might be explained by unmeasured factors like present joint inflammation, diabetic neuropathy, peripheral or central sensitization or psychological factors.

5.6.4 The prevalence of hand disorders

In paper 5 we reported the prevalence of hand disorders and body stiffness and the association to collagen Advanced glycation end products and long-term HbA1c. The point prevalence of hand diagnoses was increased compared to the control group for Dupuytrens disease, 62% vs 15% and Trigger finger, 8% vs 1% but not for Carpal tunnel syndrome, 3% vs 1%. The life-time prevalence was significantly higher for all diagnoses in the diabetes group. For Dupuytrens disease, Banon et al. suggests an increase in the prevalence with diabetes (19) but the 5 to 21% prevalence they refer to are lower than 22% prevalence in the general population reported between 50 and 89 years increasing with age to 53% in persons over 75 years in the Netherlands (83) and a mean of 21% and 29% at ages 65 and 75 found in other Western countries (76). But the diagnosis in these studies included also palpable palmar nodules alone. Only 4.2% of the patients had a flexion contracture of the fingers in the Dutch study (83) and diabetes was not found to be a significant risk factor. In earlier studies including DM1 only life-time prevalence is reported. Both Arkkila et al. (23) and Cagliero et al. (21) reported a 20% prevalence using flexion contracture as the diagnostic criterium. Larkin et al. (20)
mentioned no diagnostic criteria and found a 9% prevalence. Although the prevalence in these studies span over a wide range and partly describe unclear diagnostic criteria, the numbers are far lower than in the present study which may suggest an increase in prevalence with disease duration (figure 6).

For Trigger finger, the comparable studies reported life-time prevalence only, 20% (21) and 28% (20) while we found a 42% life-time prevalence.

For Carpal tunnel syndrome, we found no difference in point prevalence between the diabetes and control group. This was most likely due to the frequent surgical treatment in the diabetes group. The life-time prevalence reported earlier in DM1 was 11% and 30% (20, 21). With the 37% from our study the pattern mimics the life-time prevalence for Trigger finger (figure 6).

A higher age and longer duration of diabetes in the present cohort and differences in diagnostic definitions in the existing studies may have contributed to the differences in the prevalence of hand diagnoses.

![Life-time prevalence of hand diagnoses with increasing duration of DM1](image)

Figure 6. Life-time prevalence of hand diagnoses in three DM1 cohorts with 22 (21), 32 (20) and 50 (1) years disease duration.

5.6.5 **Stiffness and Advanced Glycation End products**

Numerous studies have reported stiffness in different body regions in patients with DM1 (19, 20, 22, 23). It is postulated that the glycaemic burden over years and Advanced glycation end products (AGEs) in connective tissue is associated with body stiffness (19), but few studies have examined this topic (34, 149). Some of the AGEs are known to be cross-linkers of collagen and are hypothesized to
be associated with body stiffness. To get closer to this hypothesis we decided to measure body stiffness and AGEs in collagen to evaluate a possible association. A general measure of body stiffness does not exist to our knowledge and we decided to measure typical areas (shoulder and hand) reported to cause stiffness in DM1 (19, 20) and also stiffness in the spine which is less frequently reported and only in studies with few patients (111, 112, 150). The prayer sign is a quite robust indication of stiffness in the hand because the sign is rarely seen in the normal population (79). Frozen shoulder is a diagnosis which require global stiffness in the shoulder by at least 30 degrees or a 50% reduction range of motion compared to the non-affected side or to normative values. With such criteria, the diagnosis of frozen shoulder is quite robust as well. Stiffness in the spine is more difficult to measure because the spine includes multiple synovial joints and vertebra-disc connections as well as a large number of muscles which all may contribute to spinal stiffness. The Fingertip-to-floor distance is also dependent of the relative length of arms and legs, abdominal adiposity and factors that affect the hip joints like hip osteoarthritis, tight joint capsule or short hamstring muscles. Despite these weaknesses, we chose Fingertip-to-floor distance as a measure of stiffness in the lumbar spine because it is widely used in the clinical setting, is easy and reliable to use and normative values exist (114). The difference between the diabetes and the control groups was substantial with regards to hand and shoulder stiffness. For back stiffness, the diabetes group experienced significant, but only slightly increased Fingertip-to-floor distance compared to the controls. We did not find significant associations between stiffness and age, diabetes duration, gender or micro- or macrovascular complications.

All collagen Advanced glycation end products (AGEs) were significantly higher in the diabetes group except one (MOLD). We found no significant associations between AGEs and shoulder or hand stiffness. In the diabetes group, the AGEs MOLD and pentosidine and Estimated Full Duration HbA1c were positively associated with back stiffness in the full model, while CEL was inversely associated with back stiffness. We found no comparable studies. The biopsies were taken from the nates area. The missing or weak associations between AGEs and stiffness may be explained by the site of the biopsy. We do not know whether the concentration of AGEs in skin collagen is an accurate marker for the concentration in other tissues more relevant to joint stiffness, such as tendons, ligaments, muscles and cartilage. The rate of turnover of the protein is an important factor for AGE synthesis and whereas the half-life of skin collagen is about 15 years, both tendon and cartilage collagen half-lives are much longer (up to 117 years) (151, 152).

6. CONCLUSIONS

1. The point prevalence of frozen shoulder was 59% in the diabetes group versus zero in the control group, with no difference in other shoulder diagnoses. The lifetime prevalence was 76% in the
diabetes group versus 14% in controls. The DM1 group had reduced range of motion for all measures and had higher shoulder disability scores associated with the historical HbA1c levels. In agreement with previous studies we found a weak, but significant association between FS and historical HbA1c in the diabetes group.

2. The prevalence of radiological glenohumeral osteoarthritis was higher in the diabetes group than in the control group, but few had moderate and severe osteoarthritis. The radiological findings were not associated with shoulder pain or the long-term glycaemic burden.

3. The interpretation of the shoulder x-rays showed moderate inter-tester and moderate to almost perfect intra-tester reliability. The prevalence of radiological glenohumeral osteoarthritis varied according to the classification system applied. The higher prevalence in the diabetes group was not observed for moderate to severe radiological OA and clinical glenohumeral OA. We found no association between radiological and clinical glenohumeral OA.

4. We did not find increased radiological OA in the hands in the diabetes group. The interpretation of x-rays showed excellent intra-tester reliability. The DM1 patients in our study had higher self-reported disability in the hands which was associated with higher current and long-term HbA1c.

5. The patients with DM1 had increased lifetime prevalence of hand and shoulder diagnoses and a higher point prevalence of stiffness of the hand, shoulder and low back. The stiffness was associated with the long term HbA1c. Back, but not hand or shoulder stiffness, was associated with two of the eight Advanced glycation end products examined.

7. CLINICAL INTERPRETATION AND THE NEED FOR FURTHER RESEARCH

Disability of the shoulders and hands represent a severe and lasting problem in patients with type 1 diabetes, is associated with poor glycaemic control and seem to increase with disease duration. The issue should be addressed in the care for patients with DM1 and care pathways should be established in the diabetes guidelines.

The causes of the increased musculoskeletal problems in DM1 are not evident even if painful frozen shoulder and shoulder stiffness was associated with high HbA1c. Future research should address this topic. The relation between Advanced glycation end products and stiffness is still uncertain and analyses of biopsies from affected tissue like the shoulder capsule or contracted connective tissue in the hands may give new insight.

Taken into consideration the considerable disability related to the hands and shoulders in long-term type 1 diabetes mellitus, intervention studies targeting these disabilities are warranted.
8. REFERENCES


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9. APPENDICES

1. Form used for the standardised clinical examination

2. Measurement protocol for range of motion and isometric muscle strength

3. Glycaemic index

4. Imaging procedure for shoulder and hand x-rays
### Undersøkelse - legeskjema

<table>
<thead>
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### Ledd | Undersøkelse | Resultat | Kommentar
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Høyre | Venstre
--- | --- | --- | ---
Albue | Epicondylitt | Neg(0)pos(1), jfr. diagnostisk skjema |  
Håndledd | Carpal tunnel syndrom | Neg(0)pos(1), jfr. diagnostisk skjema |  
Hånd | Prayer sign | Neg(0)pos(1) |  
 | Triggerfinger | Neg(0)pos(1)spesifisere finger |  
 | Dupuytren | Neg(0)pos(1)spesifisere finger |  
 | Fleksjon 2-4 til h.flate | Neg(0)pos(1) |  
Tommel | Pulpa 1f til 5MCP | Neg(0)pos(1) |  
Grepstyrke |  | Psi |  
Akillessene | Spoleform | Neg(0)pos(1)palpatorisk |  
 | Palp øm midtporsjon | Neg(0)pos(1)3psi |  
 | Palp øm entese | Neg(0)pos(1)3psi |  
Rygg | F-G-A | Cm |  
Nakke | O-W-D | Cm |  
Undersøker |  | 1 eller 2 |  

Diagnoseforkortelser: ingen(0) , SIS-Subcromial Impingment Syndrom(1), FS-Frozen shoulder (2), RCT-Rotator Cuff Tear(3), GHart-Glenohumeral artrose(4), ACart-AcromioClavicular artrose(5), Andre(6)
Appendix 2.

**Measurements of range of motion and isometric muscle strength**

**Range of motion**

The intra observer reliability is found to be comparable for visual estimation and manual and digital goniometers (1-3). An intra rater standard error of measurement of 3-5 degrees is found for all used measurements of shoulder motion (1).

Normative data was mainly collected from Muir et al (1) and supplemented with Hand-behind-back numbers from Ginn et al. The numbers were not age adjusted both because of missing age relevant data and the small effect of age showed by Macedo et al (4).

Active range of motion (AROM) in flexion was measured with the patient sitting on a chair with firm back, the side to the wall. The glenohumeral rotational centre of forward flexion was aligned with origo of a wall hanged measuring device with 5 degrees increments. The patient was asked to lift his straight arm with the thumb up as high as possible without bending backwards. The investigator read the AROM by aiming from the side using the patients humerus as indicator.

AROM in external rotation was measured with the patient standing with his back to the wall, arm along the side, the elbow flexed 90 degrees and the forearm pointing forwards 90 degrees to the ventral plane. A two-armed manual inclinometer with 5 degrees increments was fixed to the wall with the origo just behind and below the patients elbow and the movable arm parallel to his forearm. The patient was asked to rotate the hand outwards keeping the elbow in position and the back against the wall without rotating the body. The moved the free goniometer arm parallel to the patients forearm to measure the external rotation.

AROM in internal rotation was measured as a combined movement (hand behind back). The standing patient was asked to reach as high as possible along the spine with the thumb without bending forwards. The distance from the spinose of c7 to the thumb along the column was measured in centimeters. If the person was unable to reach the spine a horizontal line was drawn from the position of the thumb to a downwards extension of the spine and the distance to c7 was measured from here.

Passive glenohumeral range of motion (PROM) was measured with the patient seated.

PROM in external rotation was recorded with the elbow fixed along the patient’s side in 90 degrees of flexion and the hand pointing forward 90 degrees from the ventral plane. The investigator rotated
the patient's forearm externally until an elastic stop was felt and read the degrees of external rotation from above with the precision of five degrees.

For passive range of motion in abduction the investigator fixed the patient's scapula with one hand and held the patient's arm under the patient's flexed elbow with the other. Starting position was along the body. The arm was abducted in slight flexion (in the scapular plane, approximately 20 degrees of flexion) until an elastic stop was felt and the degree of abduction was read from behind with the precision of five degrees.

*Isometric muscle strength.*

The shoulder muscle strength was measured in Newton (N) (1 kg = 9.80665 N) with a hand-held dynamometer (Microfet 2, Hoggan Health Industries Inc.). The device showed the result on a digital display freezing the highest measured value. All persons had the same information and tested the routine once before the measure was done.

For abduction the straight arm was internally rotated and put in 45 degrees abduction and 20 degrees flexion (scapular plane). The dynamometer was placed at the wrist just proximal to the ulnar styloid. The persons were instructed to elevate their straight arm with as much muscle strength as possible against the fixed dynamometer and the maximum produced muscle strength was read on the display.

For external rotational muscle strength, the arm was positioned along the body with the elbow flexed 90 degrees pointing straight forward and with the forearm in neutral rotation. We placed the dynamometer at the wrist between the radial and ulnar styloid and instructed the person to rotate their hand externally with maximal muscle strength against the fixed dynamometer keeping their elbow at their side. The maximum force was read.

**References**

Appendix 3.

**Glycaemic index**

*HbA₁ and HbA₁c.*

Longitudinal HbA₁ and HbA₁c values were available from 1980 to 2015. The mean (SD) number of measurements taken per subject at different time intervals was 73. One laboratory method was used for HbA₁ (Agarose gel electrophoresis at Oslo University Hospital, Aker, Oslo, Norway) from 1981 to 1986 and two different methods for HbA₁c (Diamat® (Bio-Rad Laboratories, Hercules, CA) from 1987 to 1993 and DCA2000 analyser (Bayer Diagnostics, Tarrytown, NY) from 1993 onwards). To transform old HbA₁ for the earliest time series into HbA₁c, we identified duplicate HbA₁/HbA₁c values (taken on the same date) from 50 different subjects and found a regression formula to convert HbA₁ to HbA₁c ($HbA_{1c} = 0.526 + 0.776HbA_{1}$). We found excellent Intraclass Correlation Coefficient (ICC) of 0.94 (95% CI = 0.89-0.97) between the HbA₁ and HbA₁c values, which is in accordance with previous findings.

30-year HbA₁c.

We calculated 30-year HbA₁c as a measure of glycaemic burden, similar to the large Diabetes Control and Complications Trial and Follow-up study (DCCT/EDIC) (1). To calculate 30-year HbA₁c, we first calculated the mean HbA₁c for each year, and then the mean of these values.

*Estimated full duration HbA₁c.*

As we do not have HbA₁c values from time of diagnosis up until the 1980s, we calculated a new measure, Estimated full duration HbA₁c (figure 6). The last method might reflect the actual glycaemic burden better as we incorporated all years living with the disease. To calculate Estimated Full Duration HbA₁c we calculated the average HbA₁c from the first three years it was measured in the individual, and multiplied this by the number of years which have elapsed between diagnosis and the first measurement of HbA₁c (Estimated HbA₁c). We then multiplied the 30-year HbA₁c by the number of years of HbA₁c readings, added that figure to the Estimated HbA₁c and then divided the total figure by the number of years with diabetes.
\[
30\text{ year } HbA_{1c} = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{1}{m} \sum_{i=1}^{m} X_{HbA_{1c}i} \right)
\]

**Estimated Full Duration HbA_{1c}**

\[
= \left( \frac{1}{3} \sum_{i=1}^{3} \left( \frac{1}{m} \sum_{i=1}^{m} X_{HbA_{1c}i} \right) \right) \times \left( \text{Year of 1st } HbA_{1c} - \text{Year of diagnosis} \right) + (30\text{ year } HbA_{1c} \times n)
\]

\[
\text{Duration of type 1 diabetes in years}
\]

Equations for calculating 30-year HbA_{1c} for each individual and Estimated Full Duration HbA_{1c} for each individual. \( n \) is the number of years between the first and last HbA_{1c} tests, the last test having been carried out in 2015, \( m \) is the total number of HbA_{1c} tests per year and \( X_{HbA_{1c}i} \) is the observed value for test \( i \).

**References**

PROTOKOLL RTG SKULDRE OG HENDER – DIALONGSTUDIE

Vedlegg til røntgenhenvisning
Jeg ber om at rtg begge skulder og rtg begge hender ifm. langtidsstudie av diabetes tas iht. vedlagte protokoll / eksempelbilder da de også skal granskes systematisk i en studie.

Returadresse for CD med bilder:

Mvh
Johan C Hellund, Enhetsleder, Overlege // Muskel-skjelettradiologisk enhet Ullevål, ARN/OUS

SKULDER

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| 1. Front I:  | • Sideangivelse høyre/venstre + innad/utadrotter  
               • FRONT I: Tuberculum minor projiseres på mediale kontur av proksimale humerus caput. Fossa glenoidale friprojiseres fra caput humeri.  
               • FRONT II: Tuberculum major projiseres som laterale kontur av proksimale humerus caput. Fossa glenoidale friprojiseres fra caput humeri.  
               • På begge projeksjoner: Bløtvet rundt skulderleddet og eventuelle forkalkninger der skal kunne vurderes. I dette området må bildet ikke være for mørkt. Bruk evnt. kile! |
| 2. Front II: | Samme som l. Men arm utadrotter. |

HÅND

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                          Hånden flatt ned på kassetten. Blende ut, slik at man får med hele hånden t.o.m. distale radius/ulna. PA stråleretning. Pronerte hender.  |
|               | • Sideangivelse høyre/venstre + at PA.  
               • Inkludere distale radius/ulna, og ned t.o.m. distale phalang. Metacarpene og phalangene skal friprojiseres, med åpne leddspalter. Ingen deviasjon i håndleddet(dette sees ved at man kan trekke en ret linje gjennom radius og 2. phalang).  
               • Bløtvet rundt hånd og evt. forkalkninger der skal kunne vurderes. |
EKSEMPELBILDER RTG SKULDRE OG HENDER – DIALONGSTUDIE
Paper 1
Paper 3
Paper 4
Long term type 1 diabetes is associated with hand pain, disability and stiffness but not with structural hand osteoarthritis features – The Dialong hand study

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Abstract

Objective
To explore whether having long-term type 1 diabetes (>45 years) is associated with a higher prevalence of radiographic hand OA, erosive hand OA and increased hand pain, disability and stiffness.

Methods
In total N = 96 persons with type 1 diabetes diagnosed before 1970 were included (mean [SD] age: 62.2 [7.4], mean [SD] HbA1c: 7.43 [0.80] and N = 49 [51%] men). Regular measurements of their HbA1c were obtained till 2015. We included N = 69 healthy controls without any diabetes (mean [SD] age: 63.0 [7.0], mean [SD] HbA1c: 5.41 [0.32], N = 29 [42%] men). The groups were compared for radiographic hand OA (Kellgren-Lawrence grade ≥2 in ≥1 joint) and erosive hand OA (central erosions in ≥1 joint), Australian/Canadian index (AUSCAN) for hand pain, disability and stiffness using regression analyses adjusted for age, sex, educational level and waist circumference.

Results
We found no associations between having long term type 1 diabetes and more prevalent radiographic hand OA (OR = 0.83, 95% CI = 0.38–1.81). We found a trend towards higher prevalence of erosive hand OA in diabetes patients (OR = 2.96, 95% CI = 0.82–10.64). Strong and consistent associations were observed between long term type 1 diabetes and increased hand pain (B = 2.78, 95% CI = 1.65–3.91), disability (B = 5.30, 95% CI = 3.48–7.12) and stiffness (B = 2.00, 95% CI = 1.33–2.67). These associations were particularly strong for women and participants below the median age of 61 years.
Conclusion

Long-term type 1 diabetes was not associated with radiographic hand OA, but was strongly associated with hand pain, disability and stiffness. The association between diabetes and erosive hand OA warrants further investigation.

Introduction

Persons with hand osteoarthritis (OA) may experience pain and disability in daily life activities to a similar extent as persons with inflammatory joint diseases [1]. A good understanding of risk factors for OA is important for prevention since no disease-modifying drugs exist. Risk factors for OA may act through mechanical or systemic pathways on the joint [1,2]. Most previous studies of the etiology of OA have regarded the knee joint [3]. The knee joint is affected by high mechanical loading which may interact with obesity and related metabolic factors, making the study of isolated effects of each risk factor on the development of OA challenging.

The effects of mechanical risk factors are strongly reduced in the hand joints implying a less confounded study of systemic risk factors for OA [4]. Known risk factors for hand OA include female sex, higher age, genetic factors, previous joint injury and hypermobility, whereas the risk related to obesity and components of the metabolic syndrome such as dyslipidemia, hypertension and diabetes mellitus is still unclear [5,6]. A distinct diabetes mellitus OA phenotype has been proposed [7]. However, few studies have explored the association between diabetes mellitus and hand OA. A recent systematic review and meta-analyses showed a higher prevalence of diabetes mellitus (mainly type 2 diabetes) in persons with hand OA than in persons without [8]. The review included only two full-length articles of studies of the hand [9,10], showing an association between diabetes and hand OA particularly at younger ages [10]. Contrarily, a recent study of incident hand OA and type 2 diabetes showed no association [11].

There are several potential causal pathways through which diabetes may lead to hand OA and/or pain in hand OA. Diabetes may cause a low-grade systemic inflammation, and thereby contribute to hand-joint inflammation and pain [7]. Patients with long term diabetes may also suffer from diabetic neuropathy which may contribute to pain [12]. Furthermore, the increased formation of advanced glycation end products (AGEs) may contribute to OA by various mechanisms affecting collagen tissue and chondrocytes. The explanatory mechanisms linking diabetes mellitus to hand OA may further be dependent on the OA phenotype. We have previously shown that diabetes mellitus may be a potential cause of pain in erosive hand OA but not in non-erosive hand OA, supporting previous studies indicating a distinct metabolic/diabetes/erosive OA phenotype [6,7,13,14].

Previous studies have examined OA in persons with accumulation of several metabolic risk factors including type 2 diabetes, making it challenging to isolate the independent effect of long-term hyperglycaemia on the development of hand OA. The study of OA in a type 1 diabetes mellitus population allows for the study of the more pure effects of chronic hyperglycaemia on hand OA. Improved knowledge of the association between type 1 diabetes and hand OA/hand pain will provide important knowledge for development of preventive and disease-modifying interventions. Our aim was to explore whether having long-term type 1 diabetes is associated with a higher prevalence of radiographic hand OA, erosive hand OA and increased hand pain, disability and stiffness.
**Patients and methods**

**Participants and data collection**

The present study is a sub-study of the Dialong study, a cross-sectional, controlled, retrospective study of persons attending the Norwegian Diabetes Centre (NDC) from various time periods to 2015. The main aim of the study was to explore macrovascular and non-vascular complications in patients having long-standing type 1 diabetes for >45 years. Patients attending the NDC in 2014 with type 1 diabetes diagnosed before 1970 were invited to take part in the study as cases exposed to a long term high glycaemic burden (N = 136). The diagnosis was based on (i) clinical criteria (ii) lack of insulin production as measured by fasting c-peptide, i.e. <0.2 pmol/ml and (iii) HbA1c > 6.5%. The exposed cases were asked to invite their spouses or close friends without diabetes to participate as healthy controls in the study. Potential controls with known diabetes or undiagnosed diabetes as measured by HbA1c > 6.5% were excluded as well as first degree relatives. We also excluded participants with known inflammatory rheumatic disease in the current study.

Data were collected at two different sites in 2015, the Oslo University Hospital, Ullevål (OUHU) and the NDC. During two visits, participants had fasting blood tests, underwent conventional radiographs of the hands, responded to questionnaires and had their height, weight and waist circumference measured. Participants also underwent a clinical examination of their hands with assessment of hand complaints as well as an assessment of the presence of peripheral neuropathy at one of the visits. All patients signed informed consent and the Regional Ethical Committee South East (Regional Committees for medical and health research ethics) approved the study.

**General diabetic assessment and measurement of glycaemic burden**

We searched medical records at NDC and performed patient interviews to establish the date of diagnosis of type 1 diabetes and any co-morbidities. Most of the patients had attended the NDC since the time of diagnosis with extensive documentation of their diabetic control and complications. Longitudinal HbA₁ and HbA₁c values were available from the early 1980s up until 2015. In total, the mean (SD) number of measurements taken per subject at different time intervals was 73 (29).

Different laboratory methods were applied in different time series. One method was used for HbA₁ (Agarose gel electrophoresis at Oslo University Hospital, Aker, Oslo, Norway) from 1981 to 1986 and two different methods for HbA₁c (Diamat (Bio-Rad Laboratories, Hercules, CA) from 1987 to 1993 and DCA2000 analyzer (Bayer Diagnostics, Tarrytown, NY) from 1993 onwards). To transform old HbA₁ for the earliest time series into HbA₁c, we identified duplicate HbA₁/HbA₁c values (taken on the same date) from 50 different subjects and found a regression formula to convert HbA₁ to HbA₁c (HbA₁c = 0.526 + 0.776HbA₁). We found excellent Intraclass Correlation Coefficient (ICC) of 0.94 (95% CI = 0.89–0.97) between the HbA₁ and HbA₁c values, which is in accordance with previous findings [15].

We calculated time-weighted mean HbA₁c as a measure of glycaemic burden for the diabetes patients, similar to the large Diabetes Control and Complications Trial and Follow-up study (DCCT/EDIC) [16]. As we do not have HbA₁c values from time of diagnosis up until the 1980s, we created two different variables for each participant with long term diabetes: one that only incorporated existing values from the 1980s up till today and one that weighted the initial values with number of years from diagnosis till the first HbA₁c value (estimated full duration HbA₁c). The last method better reflected the actual glycaemic burden as we incorporated all years living with the disease and we therefore used this mean time-weighted HbA₁c as a
continuous measure of glycaemic burden in the analyses. Details of the calculations are presented in S1 Fig. All participants had HbA1c taken at OUHU (High Performance Liquid Chromatography, reference range 4.0–6.0) in 2015 (current HbA1c). Microvascular complications as a result of long term type 1 diabetes, i.e. persistent albuminuria were defined as an albumin creatinine ratio of > 2.9 mg/mmol on two consecutive samples, including the sample taken in 2015.

Conventional radiographs

The participants underwent conventional radiography (frontal images) of both hands. The bilateral first carpometacarpal (CMC-1), scaphotrapezotrapezoidal (STT), 1st-5th metacarpophalangeal joints (MCP), thumb interphalangeal (IP-1), 2nd-5th proximal interphalangeal joints (PIP) and 2nd-5th distal interphalangeal joints (DIP) were scored for radiographic OA according to a modified Kellgren-Lawrence (KL) scale [17,18] and for central erosions according to the OARSI atlas [19] by one experience reader (IKH). The modification of the KL scale refers to the scoring of definite joint space narrowing as present OA also in the absence of osteophytes ([17,18]). Hand OA was defined as involvement of ≥ 2 hand joints with Kellgren-Lawrence grade (KLG) ≥ 2), whereas central erosion in one or more of the joints was required for erosive OA. After several weeks/months, 20 x-rays were re-evaluated. The ICC values for KL sum score (0.98, 95% CI 0.95–0.99) and number of erosive joints for the bilateral hands were excellent (1.00, 0.99–1.00).

Hand pain, physical function and stiffness

Self-reported hand pain, disability and stiffness were assessed using the Australian/Canadian (AUSCAN) scale [20,21]. The scale consists of 3 subscales measuring 1) hand pain during rest and activity (5 items), 2) physical hand function during activities in daily life (9 items) and 3) hand stiffness (1 item). Each item is measured on a 0–4 numerical rating scale. Sum scores were calculated for each item and included as a continuous outcome variable in the analyses (0–20 scale, 0–36 scale and 0–4 scale, respectively). Higher score represents more pain, worse physical function and worse stiffness.

Covariates

Educational level was reported in four categories ranging from primary school to college/university and dichotomized into low (upper secondary school) vs. high education level (college/university [0–1]). Height and weight were measured wearing light indoor clothing and Body Mass Index was calculated (kg/m²). We also measured waist circumference in centimeters. All participants had their systolic and diastolic blood pressure measured and the total cholesterol and triglycerides were obtained from fasting blood samples. The presence of hand diagnoses other than OA (i.e. carpal tunnel syndrome, trigger finger, Dupuytren’s contracture and limited joint mobility of the hands) was assessed according to a standardized procedure by an experienced specialist in physical medicine and rehabilitation (NGJ). We created a categorical variable indicating 0 to 4 hand complaints (0 was the ref. category). The presence of peripheral neuropathy (yes/no) was defined based on either previously confirmed diagnosis by a positive nerve conduction test or the presence of symptoms such as numbness, unsteadiness, aching, burning pain or pins and needles, as well as symmetrical signs in both lower extremities using standard monofilament and vibration tests.
Statistical analyses

We performed secondary analyses of the Dialong study, which was initially powered to study the association between coronary artery disease and glucosepane, an advanced glycation end product in skin collagen. Hence, we had no possibility to increase the power a priori. For explorative reasons and due to previous findings with regard to erosive OA [13], we included erosive OA as an outcome despite the relatively low study sample. Prior to all analyses, we checked distributions of covariates and explored statistically significant group differences between the exposed and unexposed participants using t-tests and chi-square. To study the associations between diabetes and hand OA outcomes, we performed separate regression analyses using the presence of long-term type 1 diabetes (yes/no), the current HbA1c for cases and controls and the estimated full duration HbA1c (cases only) as continuous independent variables. The presence of radiographic OA and erosive OA (logistic regression), hand pain and disability (linear regression) as well as stiffness (ordinal regression) were included as dependent variables in separate models. We performed crude analyses, analyses adjusted for age and sex as well as fully adjusted analyses (adjusted for age, sex, educational level and waist circumference). Since persons with type 1 diabetes and proteinuria may be at higher risk of complications such as OA, we adjusted for persistent albuminuria (yes/no) in the analyses of full duration HbA1c, for cases only. We also additionally adjusted the analyses of the diabetes variables and AUSCAN hand pain, physical function and stiffness for hand complaints (carpal tunnel syndrome, trigger finger, Dupuytren’s contracture and limited joint mobility of the hands on a 0 to 4 scale) in separate analyses. Finally, we adjusted the analyses of AUSCAN hand pain for the presence of peripheral neuropathy to explore the likelihood of residual confounding. This was avoided in the main analyses since hand OA pain may be of both neuropathic and nociceptive origin.

We tested for statistical interactions by including a product term between the exposure (i.e. case-control status, current HbA1c, or estimated full duration HbA1c) and age and sex in the fully adjusted model (i.e. the model adjusted for age, sex, education status and waist circumference). If any statistically significant interactions (p < 0.10) were found, we performed analyses stratified by age (above and below median) and sex (men and women). The stratified analyses were adjusted for sex, age, education level and waist circumference. We repeated the analyses using a continuous score representing the severity of radiographic hand OA (KL sum score, 0–120). Since metabolic factors may be associated with hand OA and HbA1c/glycaemic burden, we also repeated the analyses with additional adjustment for hypertension (systolic blood pressure ≥135 mm HG and/or diastolic blood pressure ≥85 mm HG), total cholesterol and triglycerides (continuous variables) in a sensitivity analysis. This additional adjustment was not done in the main analyses as it would imply a reduced statistical power (particularly for estimated full duration HbA1c as the exposure variable and erosive hand OA as outcome variable) and a conditioning on variables that are functions of the selection process, which might open up spurious, biasing and non-causal paths. Prior to the regression analyses, we inspected plotted residuals to evaluate any deviation from a normal distribution (no strong deviations observed). Furthermore, all analyses were run with a robust standard error to account for potential heteroscedasticity. Results are presented as unstandardized beta estimates or Odds Ratios (OR) with 95% confidence intervals (CI). All analyses were performed using STATA MP v. 14. The minimal underlying dataset can be found in S1 Dataset.

Results

Out of the N = 136 cases exposed with long-term type 1 diabetes, N = 105 agreed to participate. We excluded N = 9 due to psoriatic arthritis (N = 1), rheumatoid arthritis (N = 2), lack of hand
joint examination (N = 2), lack of blood samples (N = 2) or withdrawal of consent (N = 2), leaving N = 96 persons for the analyses. In total N = 80 persons without diabetes were invited, representing healthy controls. Of these, N = 75 agreed to participate and they had no diabetes as tested by HbA1c. We excluded N = 6 persons from the diabetes-free control group due to spondyloarthritis (N = 1), psoriatic arthritis (N = 2), lack of blood samples (N = 2) or lack of hand joint examination (N = 1), leaving N = 69 for the analyses. Participants’ characteristics are presented in Table 1. The range of all participants’ HbA1c measurements was 4.4–9.9 mmol/l whereas cases’ estimated full duration HbA1c range was 5.8–9.8 mmol/l. Cases exposed to long term diabetes and the healthy controls had a similar age and sex distribution and had a similar education level, BMI and waist circumference, since there were no statistically significant differences between the exposed vs. the unexposed (p>0.05). The measured diastolic and systolic blood pressure, total cholesterol and triglycerides were significantly higher in healthy controls than in cases exposed to long term diabetes (all p<0.05).

Radigraphic hand OA

We found no association between being a case exposed to long-term type 1 diabetes or having a higher current HbA1c and having one or more joints with radiographic hand OA (Table 2).

Table 1. Participants’ characteristics.

<table>
<thead>
<tr>
<th>Sociodemographic variables</th>
<th>Cases N = 96</th>
<th>Controls N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>62.2 (7.4)</td>
<td>63.0 (7.0)</td>
</tr>
<tr>
<td>Sex, M, n (%)</td>
<td>49 (51.0)</td>
<td>29 (42.0)</td>
</tr>
<tr>
<td>Education level (high), n (%)</td>
<td>60 (62.5)</td>
<td>51 (76.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anthropometrics and metabolic covariates</th>
<th>Cases N = 96</th>
<th>Controls N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waist circumference, mean (SD)</td>
<td>91.7 (13.0)</td>
<td>89.4 (12.9)</td>
</tr>
<tr>
<td>Body Mass Index, kg/m², mean (SD)</td>
<td>26.2 (4.0)</td>
<td>25.8 (4.3)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg), mean (SD)</td>
<td>146.4 (19.9)</td>
<td>136.9 (19.9)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg), mean (SD)</td>
<td>75.2 (8.3)</td>
<td>80.9 (9.5)</td>
</tr>
<tr>
<td>Hypertension [0–1], n (%)</td>
<td>43 (62.3)</td>
<td>79 (82.3)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L), mean (SD)</td>
<td>5.0 (1.0)</td>
<td>5.8 (1.2)</td>
</tr>
<tr>
<td>Triglycerides (mmol/L), mean (SD)</td>
<td>0.9 (0.4)</td>
<td>1.1 (0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diabetes variables</th>
<th>Cases N = 96</th>
<th>Controls N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c in 2015, mean (SD)</td>
<td>7.43 (0.80)</td>
<td>5.41 (0.32)</td>
</tr>
<tr>
<td>Glycaemic burden (i.e. mean time-weighted HbA1c), mean (SD)</td>
<td>7.95 (0.81)</td>
<td></td>
</tr>
<tr>
<td>Years lived with type 1 diabetes, mean (SD)</td>
<td>50.7 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Persistent albuminuria, n (%)</td>
<td>17 (18.1)</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy, n (%)</td>
<td>62 (64.6)</td>
<td>14 (20.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Osteoarthritis variables</th>
<th>Cases N = 96</th>
<th>Controls N = 69</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kellgren-Lawrence sumscore [0–120], median (IQR)</td>
<td>10 (3–21)</td>
<td>12 (6–21)</td>
</tr>
<tr>
<td>Radiographic OA [0–1], n (%)</td>
<td>60 (62.5)</td>
<td>44 (63.8)</td>
</tr>
<tr>
<td>Non-erosive OA [0–1], n %</td>
<td>49 (81.2)</td>
<td>41 (93.2)</td>
</tr>
<tr>
<td>Erosive OA [0–1], n %</td>
<td>11 (18.3)</td>
<td>3 (6.8)</td>
</tr>
<tr>
<td>AUSCAN pain [0–20], mean (SD)</td>
<td>4.1 (4.9)</td>
<td>1.4 (2.6)</td>
</tr>
<tr>
<td>AUSCAN physical function [0–36], mean (SD)</td>
<td>7.6 (8.0)</td>
<td>2.6 (4.4)</td>
</tr>
<tr>
<td>AUSCAN stiffness [0–4], mean (SD)</td>
<td>1.3 (1.0)</td>
<td>0.4 (0.6)</td>
</tr>
</tbody>
</table>

Abbreviations: M: Males, SD: standard deviation, AUSCAN: Australian-Canadian Hand Index, OA: osteoarthritis. Radiographic OA: ≥2 joints with Kellgren-Lawrence grade 2 or more. Erosive OA: ≥1 joint with central erosions.

https://doi.org/10.1371/journal.pone.0177118.t001
Among the cases exposed to long-term type 1 diabetes, there was also no association between higher glycaemic burden and more frequent radiographic hand OA (Table 2). Similarly, no associations were found between the diabetes measures and increasing severity of radiographic hand OA using the KL sum score (range 0–120) as outcome variable ($B_{\text{exposed case}} = -0.69, 95\% \text{ CI} = -5.00–3.62, B_{\text{HbA1c}} = -1.30, 95\% \text{ CI} = -3.02–0.43, B_{\text{glycaemic burden}} = 0.05, 95\% \text{ CI} = -4.30–4.40$). Additional adjustment for persistent albuminuria in the analyses of exposed cases only did not change these results ($B_{\text{glycaemic burden}} = -0.07, 95\% \text{ CI} = -4.45–4.31$). Furthermore, the exposed cases with higher glycaemic burden did not have higher risk of radiographic hand OA or erosive hand OA when additionally adjusted for persistent albuminuria (OR = 0.89, 95\% CI = 0.44–1.73 and OR = 0.89, 95\% CI = 0.44–1.73, respectively).

There was a trend towards a higher prevalence of erosive hand OA in persons with long-term type 1 diabetes, although this tendency was not statistically significant (Table 2). No statistically significant interactions were found between any of the diabetes measures and age or sex for neither radiographic nor erosive hand OA. Additional adjustment for hypertension, total cholesterol and triglycerides did not change any results (data not shown).

### Hand pain, physical function and stiffness

Contrarily to what was observed for radiographic and erosive hand OA, we found strong and consistent associations between having long-term type 1 diabetes, higher current HbA1c levels and estimated full duration HbA1c and increased hand pain, reduced physical function and increased hand stiffness (Table 3).

The estimates were reduced after adjustment for other hand diagnoses, but the diabetes measures remained statistically significantly associated with hand pain, stiffness and function (Table 3). However, the association between glycaemic burden and AUSCAN stiffness in cases was only not any longer statistically significant after adjustment for hand complaints (Table 3). When the analyses of AUSCAN hand pain including adjustment for other hand diagnoses were additionally adjusted for the presence of peripheral neuropathy, the estimates remained more or less similar ($B_{\text{exposed case}} = 1.39, 95\% \text{ CI} = 0.02–2.77, B_{\text{HbA1c}} = 1.01, 95\% \text{ CI} = 0.41–1.63, B_{\text{glycaemic burden}} = 1.74, 95\% \text{ CI} = 0.41–3.07$). Additional adjustment for persistent albuminuria in the analyses of estimated full duration HbA1c in cases only did not change the results (in analyses also adjusted for age, sex, education and waist circumference; $B = 1.96, 95\% \text{ CI} = 0.74–3.19, B = 3.13, 95\% \text{ CI} = 0.42–2.16$).

---

**Table 2.** Associations between case-control status, HbA1c, glycaemic burden and structural hand OA features.

<table>
<thead>
<tr>
<th>Outcome: Radiographic OA</th>
<th>Crude OR (95% CI)</th>
<th>Age and sex adjusted OR (95% CI)</th>
<th>Fully adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed case (ref.: non-exposed)</td>
<td>0.95 (0.50–1.80)</td>
<td>1.08 (0.54–2.12)</td>
<td>1.11 (0.55–2.26)</td>
</tr>
<tr>
<td>HbA1c in 2015</td>
<td>0.87 (0.66–1.15)</td>
<td>0.91 (0.69–1.22)</td>
<td>0.92 (0.68–1.25)</td>
</tr>
<tr>
<td>Glycaemic burden</td>
<td>0.84 (0.49–1.45)</td>
<td>0.92 (0.53–1.59)</td>
<td>0.91 (0.47–1.77)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Erosive OA</th>
<th>Crude OR (95% CI)</th>
<th>Age and sex adjusted OR (95% CI)</th>
<th>Fully adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed case (ref.: non-exposed)</td>
<td>2.85 (0.76–10.66)</td>
<td>3.07 (0.83–11.29)</td>
<td>2.96 (0.82–10.64)</td>
</tr>
<tr>
<td>HbA1c in 2015</td>
<td>1.12 (0.80–1.56)</td>
<td>1.16 (0.80–1.66)</td>
<td>1.15 (0.79–1.67)</td>
</tr>
<tr>
<td>Glycaemic burden</td>
<td>0.88 (0.38–2.02)</td>
<td>0.88 (0.37–2.13)</td>
<td>0.91 (0.31–2.61)</td>
</tr>
</tbody>
</table>

Logistic regression analyses (fully adjusted analyses were adjusted for age, sex, education status and waist circumference), KL; Kellgren-Lawrence Grade, Glycaemic burden; mean time-weighted HbA1c (available in exposed cases only), OA; osteoarthritis, OR; odds ratio, CI; confidence intervals. Radiographic OA: present KL1–2 in ≥2 joints. Erosive OA: present erosions in ≥1 joint.

https://doi.org/10.1371/journal.pone.0177118.t002
CI = 1.31–4.94, B = 0.67, 95% CI = 0.10–1.23 for AUSCAN pain, physical function and stiffness, respectively. To avoid over-adjustment, these analyses were not adjusted for other hand diagnosis nor peripheral neuropathy). For all symptom measures, there were statistically significant interactions between age and sex for current HbA1c as well as for case/control status. In stratified analyses on age below and above median (61 years) we found a stronger association between having long-term type 1 diabetes, higher HbA1c levels and increased hand pain, reduced physical function and stiffness in the youngest participants compared to the elderly (Table 4). We further found stronger associations in women than in men for all outcomes (Table 4). We observed a significant statistical interaction with age in analyses of glycaemic burden as the independent variable and hand pain as the dependent variable in analyses of the exposed cases only. Stratified analyses showed a stronger association in participants below median age whereas there was no association in participants above (B = 2.77, 95% CI = 1.06–4.49 and B = 0.51, 95% CI = -1.31–2.34, respectively). No age or sex differences were observed for physical function or stiffness when using glycaemic burden as the exposure variable (p > 0.10 for product term). Additional adjustment for hypertension, total cholesterol and triglycerides did not change any of the observed associations (data not shown).

**Discussion**

In the current study we found no association between having type 1 diabetes and radiographic hand OA. However, we found a tendency towards a higher prevalence of erosive hand OA in patients with type 1 diabetes as compared to healthy controls. Long-term type 1 diabetes and

<table>
<thead>
<tr>
<th>Outcome: Hand pain (0–20 scale)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude B (95% CI)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Exposed case (ref.: non-exposed)</td>
</tr>
<tr>
<td>HbA1c in 2015</td>
</tr>
<tr>
<td>Glycaemic burden</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Hand disability (0–36 scale)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude B (95% CI)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Exposed case (ref.: non-exposed)</td>
</tr>
<tr>
<td>HbA1c in 2015</td>
</tr>
<tr>
<td>Glycaemic burden</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome: Hand stiffness (0–4 scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude B (95% CI)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Exposed case (ref.: non-exposed)</td>
</tr>
<tr>
<td>HbA1c in 2015</td>
</tr>
<tr>
<td>Glycaemic burden</td>
</tr>
</tbody>
</table>

* Linear regression analyses. 
** Ordinal regression analyses. Cases exposed to long-term type 1 diabetes (N = 96), non-exposed are healthy controls (N = 69). Fully adjusted analyses were adjusted for age, sex, education status and waist circumference. Fully adjusted +adjusted for hand complaints were additionally adjusted for the presence of the hand complaints carpal tunnel syndrome, trigger finger, Dupuytren’s contracture and limited joint mobility on a 0–4 scale. Glycaemic burden; mean time-weighted HbA1c (available for exposed cases only), B; unstandardized Beta estimate, CI; confidence intervals. 
* implies p<0.05.
higher full duration HbA1c, i.e., increased glycaemic burden were strongly and consistently associated with increased hand pain, a reduced physical function and stiffness. These associations were particularly strong for women and participants below the median age of 61 years.

Strengths of the study were the extensive measurements of HbA1c in persons with type 1 diabetes giving a detailed estimate of total glycaemic burden. The cases had been exposed to a high glycaemic burden over more than 45 years and the inclusion of healthy controls with a similar age and sex distribution allows for comparison to persons without the exposure. To our knowledge, the current study is the first study of type 1 diabetes and OA, allowing for a more isolated analysis of the independent effect of chronic hyperglycaemia as measured by HbA1c levels that is not confounded through other metabolic factors.

We could find no previous study of type 1 diabetes and OA for comparison of our findings. However, if disease mechanisms due to increased HbA1c levels are similar in type 1 and type 2 diabetes (i.e., not mediated through, or affected by other metabolic factors), our study both contradicts and supports previous findings. A recent systematic review and meta-analysis found a significantly higher frequency of diabetes in OA patients than in persons without OA [8]. Based on only 3 studies, significant associations to hand OA (OR = 1.31, 95% CI = 1.07–1.61) were observed [8]. The included studies for the meta-analyses considered mainly cross-sectional prevalence data and the (type 2) diabetes could also be hypothesized to be an effect of a sedentary lifestyle due to co-occurring knee and hand OA [22]. Unlike the review, a recent large population based study of incident hand OA in 27,000 subjects found no associations to hand OA defined by primary care records [11], which is in accordance with our findings. Although relying on fewer participants, we were able to distinguish between structural OA damage and patient-reported pain, disability and stiffness showing marked differences in observed associations. To our knowledge, the dependency on age and sex for hand pain, disability and stiffness has not been previously observed.

There was a tendency to a higher prevalence of erosive hand OA among the cases exposed to long term type 1 diabetes (Table 1), which is in accordance with our previous findings for

Table 4. Age and sex stratified analyses for the association between long term type 1 diabetes and hand pain, disability and hand stiffness.

<table>
<thead>
<tr>
<th>Exposure: Current HbA1c</th>
<th>AUSCAN pain B (95% CI)</th>
<th>AUSCAN physical function B (95% CI)</th>
<th>AUSCAN stiffness B (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casex exposed to diabetes vs. healthy control (ref.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>4.18 (2.35–6.00)*</td>
<td>7.66 (4.64–10.67)*</td>
<td>2.78 (1.68–3.89)*</td>
</tr>
<tr>
<td>Men</td>
<td>0.94 (-0.25–2.13)</td>
<td>2.05 (0.52–3.58)*</td>
<td>1.10 (0.18–2.03)*</td>
</tr>
<tr>
<td>&lt;61 years</td>
<td>4.48 (2.05–6.91)*</td>
<td>6.90 (3.32–10.48)*</td>
<td>2.59 (1.32–3.86)*</td>
</tr>
<tr>
<td>≥61 years</td>
<td>1.57 (0.26–2.88)*</td>
<td>3.79 (1.64–5.95)*</td>
<td>1.59 (0.74–2.43)*</td>
</tr>
<tr>
<td>Exposure: Current HbA1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>1.88 (1.05–2.71)*</td>
<td>3.31 (1.93–4.68)*</td>
<td>1.20 (0.75–1.66)*</td>
</tr>
<tr>
<td>Men</td>
<td>0.91 (0.26–1.55)*</td>
<td>1.27 (0.49–2.04)*</td>
<td>0.63 (0.21–1.05)*</td>
</tr>
<tr>
<td>&lt;61 years</td>
<td>2.03 (1.25–2.82)*</td>
<td>2.88 (1.64–4.12)*</td>
<td>1.17 (0.74–1.60)*</td>
</tr>
<tr>
<td>≥61 years</td>
<td>0.75 (0.06–1.45)*</td>
<td>1.63 (0.55–2.71)*</td>
<td>0.65 (0.24–1.06)*</td>
</tr>
</tbody>
</table>

* Linear regression analyses,  
| ordinal regression analyses. Cases exposed to long-term type 1 diabetes (N = 96), non-exposed are healthy controls (N = 69). Estimates are from analyses adjusted for age, sex, educational status and waist circumference (Hence, sex-stratified analyses were adjusted for age, and age-stratified analyses were adjusted for sex as well as residual confounding by age). AUSCAN; Australian-Canadian Hand Index, B; unstandardized Beta estimate, CI; confidence intervals.  
| implies p<0.05.

https://doi.org/10.1371/journal.pone.0177118.t004
self-reported diabetes [13]. In contrast, none of the 34 patients with erosive hand OA in the Oslo hand OA cohort had self-reported diabetes, whereas 6/31 (19%) of the patients with non-erosive disease reported to have diabetes [23]. Both studies are hampered by small study samples. Erosive hand OA in the general population is rather uncommon with a prevalence of 9.8% and 3.6% in women and men between 40–84 years, respectively [18]. With an erosive OA prevalence of n = 3/69 (4%) (in controls) and n = 11/96 (12%) (in cases) in the current sample, we might have included too few participants for performing any robust analyses of the association between type 1 diabetes and erosive hand OA and the potential associations between long term type 1 diabetes and erosive hand OA should be further studied in larger samples.

The increased prevalence of hand pain, disability and stiffness in the present group of patients with long term type 1 diabetes was not explained by radiographic hand OA. Similarly, although the magnitude of the estimates was greatly reduced, long term type 1 diabetes was significantly and consistently associated with hand pain, disability and stiffness even after adjustment for the diagnoses: carpal tunnel syndrome, trigger finger, Dupuytren’s contracture and limited joint mobility of the hand. These complaints have previously been shown to have increased prevalence in persons with diabetes [24] and their prevalence in the Dialong study population will be described elsewhere (work in progress). The estimates for AUSCAN hand pain were also only slightly attenuated after adjustment for peripheral neuropathy, implying other, unmeasured factors might explain the association between type 1 diabetes and the AUSCAN variables. As an example, we had no information on e.g. present joint inflammation, peripheral or central sensitization. Furthermore, psychological factors might have influenced our findings. Hence, future studies should further explore explanatory factors for the strong associations between long term type 1 diabetes and increased hand pain, reduced physical hand function and increased stiffness.

Our study had some weaknesses. First, we had too low power to detect any statistically significant differences between cases and controls for erosive hand OA. Our post hoc power analyses revealed that N = 133 participants per group would be required to detect any difference with the observed proportions affected. For radiographic hand OA in ≥2 joints, we observed equal proportions affected in the exposed versus unexposed group. N = 79 subjects per group would be required to detect a 20% difference in prevalence with 80% power at a 5% significance level. Similarly, as an example for KL sum score, indicating amount and severity of radiographic OA ranging from 0 to 120, N = 86 participants per group would be required to detect a difference of 6 units (with observed SD 14 and 80% power at a 5% significance level) [25]. For AUSCAN pain and physical function, the differences between exposed and unexposed were greater than proposed cut-offs for minimally clinically relevant differences (1.49 for AUSCAN pain and 1.25 for AUSCAN physical function) [26], and we concluded we had sufficient power for all outcomes except erosive hand OA. A second weakness of the study is that the cases attending the NDC having HbA1c measures available for calculation of glycaemic burden may have a slightly less severe disease than persons not attending. The cases were compared to the National Norwegian Diabetes Register showing persons with type 1 diabetes in the same diabetes duration and age as our participants had a mean HbA1c of 7.6% in 2015 [27]. With a mean current HbA1c of 7.4% in our study we might have underestimated the true associations. The selected controls, who were spouses and friends to the patients, may also not be representative to a general population, introducing additional selection bias. We observed a significantly higher blood pressure, total cholesterol and triglycerides among controls than among cases, which might be due to the more frequent use of HMG-CoA reductase inhibitors by the exposed cases (53.3% vs. 16.2%, respectively). However, according to standard epidemiological methods, a control group should not be free of exposure, but similar to the population the researcher wants to make inference about. As an example, the blood pressure and BMI of
the controls was similar to, or slightly lower than that observed in a study population representative for the Norwegian population [28], which we believe minimizes the risk of skewed selection having biased our results. A third weakness of our study is our calculation of time-weighted mean HbA1c. The methods for measuring HbA1c were developed around 1980. Our first values are therefore taken in the early stages of the study with probable lower validity and reliability before an international standard of measurement was established (the US based “National Glycohemoglobin Standardization Program” (NGSP) in 1996). To compensate for this, we calculated the average of the years without HbA1c readings from the first three years rather than the first single reading. We therefore cannot say whether our calculations are over- or under-representing the actual HbA1c values up until the 1980s. Nevertheless, we believe giving more weight to the early values taken before the universal introduction of intensive insulin-treatment, better reflects the full duration of diabetes. A final limitation of our study was the lack of data on occupation. Some studies indicate people with work tasks involving extensive use of the hands might be more affected by hand OA [29]. However, the high level of education in both study groups makes this assumption less likely.

In conclusion, the current study showed that long term type 1 diabetes was not associated with radiographic hand OA, but was strongly associated with increased hand pain, hand stiffness and reduced hand function, particularly in women and young participants with higher HbA1c. The association between diabetes and erosive hand OA should be further explored using larger sample sizes.

Supporting information
S1 Fig. Equations for calculating Mean Time-Weighted HbA1c for each individual (MTW) and Full Duration Mean Time-Weighted HbA1c for each individual (FDMTW).
(DOCX)

S1 Dataset. Minimal data set underlying the findings in the study.
(DTA)

Acknowledgments
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Conceptualization: KM TJB K. B. Hagen IKH NGJ JIB.
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Formal analysis: KM K. B. Holte.
Funding acquisition: TJB K. B. Hagen KM.
Investigation: KM K. B. Holte.
Methodology: KM K. B. Holte.
Project administration: TJB KM.
Resources: TJB NGJ JIB.
Validation: IKH TJB K. B. Holte.
Writing – original draft: KM.
References


Writing – review & editing: KM TJB K. B. Hagen K. B. Holte IKH NGJ JIB.
Paper 5