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The prevalence of radiological glenohumeral osteoarthritis in long-term type 1 diabetes: the Dialong shoulder study

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Objectives: This study compares the prevalence of radiological osteoarthritis (OA) in patients with type 1 diabetes mellitus (DM1) for > 45 years and controls, and explores the association with shoulder pain and glycaemic burden in patients with DM1.

Method: 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 glycosylated haemoglobin (HbA_{1c}) 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 \pm sd duration of DM1 was 50.6 ± 4.8 years, mean 30 year HbA_{1c} 7.4%, and age 61.9 ± 7.1 years. The mean age of controls (57% women) was 62.6 ± 7.0 years. Radiological glenohumeral OA was found in 36 diabetes patients (35%) and 10 controls (14%) [odds ratio (OR) 3.4, 95% confidence interval (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 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 HbA_{1c}) in the diabetes group ($p > 0.2$).

Conclusions: Radiological glenohumeral 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.

Microvascular and macrovascular complications in type 1 diabetes mellitus (DM1) are related to the degree of long-term glycaemic control (1, 2). With intensified insulin treatment improving blood glucose control, more patients have normal life expectancy and consequently many patients have now lived with DM1 for more than 50 years. Diabetes is a risk factor for developing adhesive capsulitis (frozen shoulder) (3). Shoulder pain and stiffness have been reported to affect as many as 31% of those with long-lasting DM1 (4). We recently showed a point prevalence of frozen shoulder of 59% in the present cohort of patients with DM1 for > 45 years (5).

A systematic review and meta-analysis including mainly patients with type 2 diabetes reported an association between diabetes and osteoarthritis (OA) (6). The metabolic syndrome, with overweight, systemic inflammatory,

and adipose tissue-related components, may contribute to this association (7, 8).

OA in the glenohumeral joint is rare in the general population. Two studies have reported the prevalence in random samples of community-dwelling people aged > 65 years. Cho et al (9) reported a prevalence of 5.0% in a Korean population using the Kellgren–Lawrence (KL) classification (10), defining grade 2 and higher as OA. Kobayashi et al (11) used the Samilson–Prieto classification (12) and found a prevalence of 17.4% in a Japanese population of the same age. Kobayashi et al, but not Cho et al, found that the risk of OA increased with age. We have not identified any studies reporting the prevalence of glenohumeral OA in people with DM1, in particular not in patients with long-lasting DM1.

The primary aim of the present study was to compare the prevalence of radiological glenohumeral OA according to the KL classification in patients with DM1 and controls. The secondary aim was to explore the association between radiological OA and shoulder pain on abduction or worst pain reported last week. In the diabetes group, the association between long-term glycaemic burden and OA was also explored.

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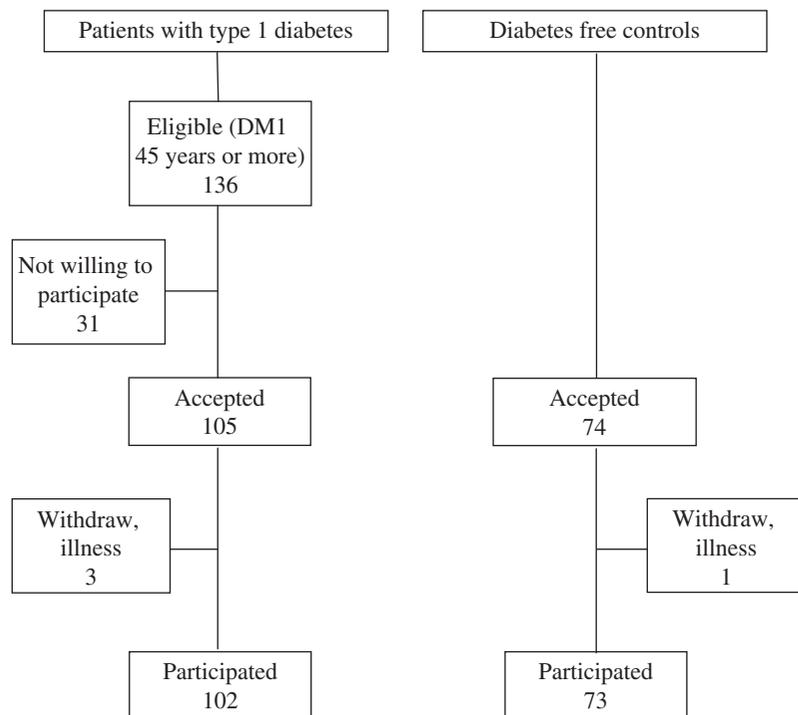


Figure 1. Inclusion of patients and controls. DM, diabetes mellitus.

Method

We conducted a cross-sectional, controlled study including patients who had had DM1 for > 45 years and a control group without diabetes, as part of the Dialong study. Written, informed consent was obtained from all subjects willing to take part in the study. Approval for the study was obtained from the Regional Ethics Committee for Medical and Health Research Ethics South-East (project no. 2014/851).

Subjects

Inclusion criteria were all patients attending the Norwegian Diabetics Center (NDC) in Oslo, Norway, in 2015 with DM1 since 1970 or earlier. Patients who were not able to cooperate in the clinical examination owing to recent trauma or severe cerebrovascular disease were excluded. Enrolled patients were asked to bring their spouses or close friends to act as controls in the study. The controls had to be free of diabetes, as confirmed by a current glycosylated haemoglobin (HbA_{1c}) level < 6.5%. First degree relatives were excluded.

Data collection

Descriptive data were collected through questionnaires, interviews, and the NDC's medical records. Educational level was reported in five categories, ranging from primary school to college/university, and dichotomized into low (upper secondary school) versus high educational level (college/university). Smoking was reported in three

categories: current smoker, past smoker, and never smoked. Body mass index (BMI) was calculated (kg/m²) and waist circumference measured (cm). The patients' files were checked for any mention of rheumatic disease.

A shoulder-specific questionnaire including the worst pain experienced last week, using a numeric rating scale (NRS) of 0–10 (10 = worst possible pain), was filled in by the study subjects. Pain is considered an important feature of most shoulder diagnoses (13). Patients with chronic shoulder pain are more prone to specify pain on this question, which helps to identify patients with painful OA. One experienced medical doctor blinded to group affiliation conducted a standardized clinical examination including range of motion. The perceived pain on active abduction was reported by the patient (NRS 0–10). All subjects had shoulder X-rays and blood samples taken. Historical HbA_{1c} data for 30 years or more were collected from patient files at the NDC for calculation of the glycaemic index. Plain X-rays were taken in the same laboratory for all participants. We used two standard anteroposterior projections with maximal external and internal rotation in the glenohumeral joint. One experienced radiologist blinded to group affiliation evaluated the X-rays.

Shoulder outcomes

The number of patients with OA KL grade 2 or more in one or both shoulders was chosen as the primary outcome, in accordance with earlier studies (9, 14). The KL classification (10) divides OA into five grades: 0 = normal, 1 = questionable, 2 = incipient or mild (slight narrowing of the joint space), 3 = moderate (distinct

narrowing of the joint space, bone cysts, and sclerosis), and 4 = severe (severe structural disorders of the joint). Agreement has been found to be acceptable, with a Cohen's weighted kappa of 0.72 (14) and 0.74 (15) for interrater reliability and 0.89 for intrarater reliability (15). We also report the number of patients with bilateral OA and the number with severe OA (KL grades 3–4). Subjects with radiological OA KL grade 2 or more in one or both shoulders and shoulder pain (worst pain last week \geq grade 2 or pain on abduction \geq grade 2) are reported as having painful shoulder OA.

Glycaemic index

HbA_{1c} was measured in 2015 (current HbA_{1c}) at the Oslo University Hospital Ullevål, using high-performance liquid chromatography (Variant; Bio-Rad, Richmond, CA, USA), with a reference range of 4.0–6.0% and an intra-assay coefficient of variation of < 3%. All HbA_{1c} measurements are reported in Diabetes Control and Complication Trial (DCCT) units (%). The '30 year HbA_{1c}' was the mean time-weighted HbA_{1c} of all HbA_{1c} measured in the individual from 1980 to 2015; the 'estimated full duration HbA_{1c}' also incorporated the unknown mean HbA_{1c} from diagnosis to the first measurement by extrapolating from the mean of the first 3 years of measurement (5). We compared our measurements with those from the national Norwegian Diabetes Register (NDR) for DM1 in adults to assess whether the diabetes patients attending the NDC were representative of the Norwegian population (16).

Statistical methods

Sample size. Based on power analysis (type I error 5%, power of 90%, expected prevalence in the diabetes

group of 35%, and the observed prevalence in an earlier comparable group of 5%) (9), we needed 56 participants in each group to detect a significant difference in the prevalence of glenohumeral OA. The observed adjusted odds ratio (OR) indicates that the best estimate in the study sample is that radiological glenohumeral OA is about four times more frequent in people with long-term diabetes than in the general population.

Analyses. Baseline characteristics are presented as mean \pm sd, median, or number (%). The risk of developing glenohumeral OA in the groups was estimated by ORs with 95% confidence interval (CI). Logistic regression was used to control for gender, age, BMI, waist circumference, and smoking. Differences between groups with and without radiological OA for the different measures of glycaemic burden were analysed using the Student's t-test, reporting the mean difference with 95% CI. We used the statistical package IBM SPSS version 23 (IBM Corp., Armonk, NY, USA).

Results

In 2015, 136 patients with DM1 for > 45 years were registered at the NDC. All patients were asked to participate in the study and 105 accepted. Three did not attend the examination because of illness. Thus, 102 patients (77%) (mean age 61.9 years, range 49–77 years) were examined together with 73 people without diabetes (mean age 62.6 years, range 50–81 years) (Figure 1). The mean duration of diabetes was 50.6 years (range 45–67 years) (Table 1).

In the diabetes group, 36 patients (35.3%) had radiological glenohumeral OA KL grades 2–4 compared with 10 subjects (13.7%) in the control group (OR 3.4, 95% CI 1.6 to 7.5; $p = 0.002$). In the diabetes group, 23

Table 1. Demographic data and comorbidity.

	Diabetes group (N = 102)	Control group (N = 73)	p
Age (years), mean \pm sd (range)	61.9 \pm 7.1 (49–77)	62.6 \pm 7.0 (50–81)	0.4
Females, n (%)	50 (49.0)	41 (56.9)	0.4
Duration of diabetes (years), median (range)	49 (45–67)		
HbA _{1c} (%), mean \pm sd	7.44 \pm 0.79	5.48 \pm 0.28	< 0.001
BMI (kg/m ²), mean \pm sd	26.2 \pm 4.0	25.8 \pm 4.3	0.5
Waist circumference (cm), mean \pm sd	91.7 \pm 13.0	89.8 \pm 13.1	0.3
Smoking, n (%)			0.3
Current smokers	5 (4.9)	8 (11.0)	
Past smokers	39 (38.2)	26 (35.6)	
Never smoked	57 (56.0)	39 (54.0)	
Education level, college or higher, n (%)	54 (74.0)	63 (61.8)	0.1
Comorbidity, n (%)			
Rheumatoid arthritis	1 (1.0)	0	0.4
Polyosteoarthritis	3 (2.9)	5 (6.8)	0.2
Psoriasis arthritis	0	4 (5.5)	0.04

HbA_{1c}, glycosylated haemoglobin; BMI, body mass index.

Table 2. Patients with radiological glenohumeral osteoarthritis (OA).

	Diabetes* (N = 102)	Control* (N = 73)	OR (95% CI)	p
Painful shoulders	39 (38.8)	19 (26.0)	1.8 (0.9 to 3.4)	0.1
OA (KL† 2–4)	36 (35.3)	10 (13.7)	3.4 (1.6 to 7.5)§	0.002
Bilateral OA (KL 2–4)	23 (22.6)	2 (2.7)	10.3 (2.4 to 45.4)	< 0.001
Painful‡ OA (KL 2–4)	15 (14.7)	2 (2.7)	5.4 (0.6 to 47.9)§	0.1
Bilateral painful‡ OA (KL 2–4)	2 (2.0)	1 (1.3)	1.44 (0.1 to 16.2)	1.0
Severe OA (KL 3–4)	7 (6.9)	1 (1.3)	5.3 (0.6 to 44.1)	0.1
Painful‡ severe OA (KL 3–4)	2 (2.0)	1 (1.3)	1.44 (0.1 to 16.2)	1.0

*Data are shown as n (%).

†KL, Kellgren–Lawrence classification, grade 2–4 defined as radiological OA, grade 3–4 as severe radiological OA. ‡Patients with both radiological OA and pain (numeric rating scale 3/10 or more) on active abduction or worst pain last are categorized as having painful OA. §Logistic regression; adjusted OR for gender, age, body mass index, waist circumference, and smoking. OR, odds ratio; CI, confidence interval.

patients (22.6%) had bilateral OA KL grades 2–4 versus two subjects (2.7%) in the control group (OR 10.3, 95% CI 2.4 to 45.4; $p < 0.001$). In the diabetes group, 39 patients (38%) reported shoulder pain, of whom 15 had radiological OA (41% of the painful shoulders). In the control group, 19 subjects (26%) had shoulder pain and two (20% of the painful shoulders) of these had radiological OA. Fifteen (14.7%) of the diabetes patients had painful OA versus two controls (2.7%) (adjusted OR 5.4, 95% CI 0.6 to 47.9; $p = 0.13$).

Seven (6.9%) of the diabetes patients had OA KL grades 3–4 (severe OA) versus one subject (1.3%) in the control group (OR 5.3, 95% CI 0.6 to 44.1; $p = 0.09$). Two diabetes patients (2.0%) and one control (1.3%) with severe radiological OA had painful OA (OR 1.44, 95% CI 0.1 to 16.2; $p = 1.0$) (Table 2). Having frozen shoulder did not increase the odds for having OA in the diabetes group (OR 0.60, 95% CI 0.26 to 1.40; $p = 0.24$).

In the diabetes group, three different measures of the glycaemic burden were used, which are given as percentage \pm sd. The mean current HbA_{1c} (%) was 7.44 ± 0.79 , the mean 30 year HbA_{1c} was 7.86 ± 0.75 , and the mean estimated full duration HbA_{1c} was 7.96 ± 0.79 . The

mean difference (%) between subjects with OA KL grades 2–4 and without OA was 0.16 (95% CI -0.49 to 0.16; $p = 0.3$) for the current HbA_{1c}, 0.19 (95% CI -0.49 to 0.12; $p = 0.2$) for the mean 30 year HbA_{1c} and 0.22 (95% CI -0.54 to 0.10; $p = 0.2$) for the estimated full duration HbA_{1c}. Subjects with severe radiological OA KL grades 3–4 did not have significantly higher HbA_{1c} levels than those without OA (Table 3). There were no significant differences in the glycaemic measures for the subjects with bilateral OA compared with those with OA in one shoulder or people without OA (data not shown). The mean \pm sd current HbA_{1c} of $7.44 \pm 0.79\%$ was not significantly different from the reported mean HbA_{1c} in 2015 in the NDR of patients with DM1 for > 45 years (7.60%, $p = 0.08$).

Discussion

In the present study, 35% of the patients with DM1 for > 45 years had radiological glenohumeral OA KL grade 2 or higher compared with 14% in the control group. The prevalence in the control group was about twice that reported by Cho et al in a Korean population aged

Table 3. Glycaemic burden in patients with and without glenohumeral osteoarthritis (OA) in the diabetes group.

Glycaemic burden	KL grade (n)	Mean	Mean difference (95% CI)	p
Current HbA _{1c}	No OA (66)	7.38	-0.16 (-0.49 to 0.16)	0.3
	KL 2–4 (36)	7.55		
	KL 3–4 (7)	7.36		
30 year HbA _{1c}	No OA (66)	7.80	0.09 (0.53 to 0.71)*	0.3
	KL 2–4 (36)	7.98		
	KL 3–4 (7)	7.64		
Estimated full duration HbA _{1c}	No OA (66)	7.88	-0.19 (-0.49 to 0.12)	0.2
	KL 2–4 (36)	8.10		
	KL 3–4 (7)	7.84		
			0.24 (-0.34 to 0.82)*	0.3
			-0.22 (-0.54 to 0.10)	0.2
			0.13 (-0.49 to 0.75)*	0.7

KL, Kellgren–Lawrence classification; HbA_{1c}, glycosylated haemoglobin, given in %. *Difference in HbA_{1c} between subjects without OA and subjects with OA, KL 3–4.

> 65 years (9) using the same radiological classification of OA. This observed difference may be related to different ethnicity, different physical workload, higher mean age in the Korean population, selection bias due to the relatively small sample size in this study, or chance (17).

The KL classification was developed for knee and hip OA and has been criticized as inappropriate for the non-weight-bearing glenohumeral joint (14, 15) because of the difficulty in classifying the minor joint space narrowing required for grade 2 OA. We cannot exclude that the use of the KL classification may have underestimated the true incidence of shoulder OA. A study using the Samilson–Prieto classification reported a higher prevalence of glenohumeral OA in the general population (11), and the use of this classification might also have increased the prevalence of OA in the present cohort. In contrast, when applying KL grade 3 as a cut-off for OA in the present study, only 7% of patients in the diabetes group and 1% in the control group had OA. Accordingly, the majority of the subjects with radiological OA in the present study were classified with mild OA.

Pain

In total, 41% of the diabetes patients and 20% of the controls with OA reported shoulder pain. Pain was not related to the severity of radiological glenohumeral OA and only two out of seven diabetes patients with severe radiological OA experienced pain. This lack of association between the severity of radiological OA and shoulder pain has been reported previously (11, 18). One possible explanation for this lack of association is the absence of synovitis, which is known to be associated with joint effusion, pain, and stiffness, and is the reason for using the term osteoarthritis instead of osteoarthrosis (8). However, the number of patients in the present study was too small to make an inference about pain and the severity of OA.

For knee and hand OA, but not hip OA, a weak association with having diabetes has been reported mainly in patients with type 2 diabetes (6, 7). However, the HbA_{1c} levels and the association between glycaemic burden and OA were not reported in those studies.

Glycaemic burden

In the present study, we did not find an association between OA and glycaemic burden as estimated by cross-sectional HbA_{1c} or 30 year HbA_{1c}. If glycaemic burden were likely to be a risk factor for glenohumeral OA, the present study should have been able to detect this from its long observation period.

Factors associated with glenohumeral arthrosis

We found no associations between OA and age, gender, weight, BMI, or long-term HbA_{1c}. Whether glenohumeral

OA increases with age is controversial (9, 11). We found no association between age and OA within the age range of 49–81 years in either the diabetes or control group. A history of shoulder trauma and especially dislocation of the glenohumeral joint is known to be a risk factor for OA (19), although Kobayashi et al did not find that the presence of a history of trauma was a risk factor for shoulder OA (11). An incidence rate of 56 per 100 000 person-years for shoulder dislocation is reported in Norway (20). Accordingly, we would expect approximately 3% of our cohort to have experienced a dislocation. We do not have data on shoulder trauma and dislocations in the present study. Although obesity is known to be a risk factor for OA in other joints, particularly in the knee (21), we did not find an association between OA and BMI. Possible explanations could be that the glenohumeral joint is non-weight-bearing and that the study population was not particularly obese. Frozen shoulder was prevalent in the diabetes group but we found no association between OA and frozen shoulder. Large rotator cuff tears may predispose to OA, but the prevalence of such tears was low in the present population and did not differ between the groups (5). Diabetic neuropathy is a frequent complication in diabetes and is associated with arthropathy in the feet, but the shoulder is rarely affected (22), making it an unlikely explanation for the high prevalence of OA found in the present study.

Another possible mechanism for the observed increased radiological OA in DM1 is elevated levels of advanced glycation end-products (AGEs). AGEs, and especially pentosidine, deposit in cartilage and other collagen tissues in joints. This may alter the collagen cross-linking and the tissue's biomechanical properties (23, 24). These changes are shown in *in vitro* models, but not in clinical studies (25). In a small controlled study, it was reported that the level of pentosidine was also increased in subchondral tissue harvested during knee replacement in patients with diabetes compared with controls (26).

The gene *Gdf5* was shown to be associated with OA, which suggests an interaction between OA and DNA methylation (27) in knee and hip OA (28). A recent study reported that different genetic control mechanisms exist in the shoulder, hip, and knee (29). At present, we have no specific knowledge to link the increased prevalence of radiological glenohumeral OA in the present study to genetic factors in patients with DM1.

Limitations

The present study included a relatively small number of subjects, which increases the probability of a false-negative association between radiological OA and long-term diabetes. The risk of observing a false-positive association is smaller but cannot be excluded. About 80% of the invited target population was examined and we do not have any information about shoulder pain and OA in the remaining individuals. Previous shoulder injury was not recorded, which could have influenced the prevalence of OA in both groups.

The use of the KL classification may underestimate the true incidence of glenohumeral OA. The use of only one interpreter and the lack of reliability measurements may have biased the reported prevalence both ways.

Generalizability

Although patients with DM1 are mostly treated in specialized diabetes outpatient clinics, the results from this study may apply to other healthcare providers consulted for medical conditions other than diabetes.

Conclusions

The present study reports a high prevalence of mild, but not moderate and severe radiological glenohumeral OA in patients with DM1 for > 45 years. The increased prevalence of radiological OA was not associated with an increase in shoulder pain or higher current or long-term HbA_{1c}.

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