Original Article
Complications

Diabetes Metab J 2023;47:869-878
https://doi.org/10.4093/dmj.2022.0275
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

The Risk of Shoulder Adhesive Capsulitis in Individuals with Prediabetes and Type 2 Diabetes Mellitus: A Longitudinal Nationwide Population-Based Study

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Background: This study aimed to investigate the association between type 2 diabetes mellitus (T2DM) and shoulder adhesive capsulitis (AC) using a large-scale, nationwide, population-based cohort in the Republic of Korea.
Methods: A total of 3,471,745 subjects aged over 20 years who underwent a National Health Insurance Service medical checkup between 2009 and 2010 were included in this study, and followed from the date of their medical checkup to the end of 2018. Subjects were classified into the following four groups based on the presence of dysglycemia and history of diabetes medication: normal, prediabetes, newly diagnosed T2DM (new-T2DM), and T2DM (claim history for antidiabetic medication). The endpoint was new-onset AC during follow-up. The incidence rates (IRs) in 1,000 person-years and hazard ratios (HRs) of AC for each group were analyzed using Cox proportional hazard regression models.
Results: The IRs of AC were 9.453 (normal), 11.912 (prediabetes), 14.933 (new-T2DM), and 24.3761 (T2DM). The adjusted HRs of AC in the prediabetes, new-T2DM, and T2DM groups were 1.084 (95% confidence interval [CI], 1.075 to 1.094), 1.312 (95% CI, 1.287 to 1.337), and 1.473 (95% CI, 1.452 to 1.494) compared to the normal group, respectively. This secular trend of the HRs of AC according to T2DM status was statistically significant ($P<0.0001$).
Conclusion: This large-scale, longitudinal, nationwide, population-based cohort study of 3,471,745 subjects confirmed that the risk of AC increases in prediabetic subjects and is associated with T2DM status.

Keywords: Diabetes mellitus; Incidence; Prediabetic state; Risk factors; Shoulder; Stiffness

INTRODUCTION

Shoulder adhesive capsulitis (AC) is a common disease characterized by a progressive and painful loss of passive and active shoulder range of motion. The prevalence of AC is between 2% and 5% in the general population and the majority of patients are female [1]. AC is a painful shoulder disease in which chronic inflammation of the capsule causes capsular thickening, fibrosis, and adhesion of the capsule to the surrounding soft tissue and anatomic neck of the humerus [2].

Systemic conditions such as diabetes mellitus (DM), obesity, dyslipidemia, thyroid disease, cardiac disease, Dupuytren con-

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Received: Aug. 7, 2022; Accepted: Dec. 11, 2022

tracture, breast cancer treatment, and neurologic disorders increase the risk of AC [1-9]. Diabetic patients have a 2 to 4-fold higher risk of developing AC compared to the general population [10]. A nationwide, population-based cohort study [9] performed in Taiwan revealed that the incidence of AC in a DM cohort was 3.08 times that of the comparison cohort (146.9 vs. 47.7 per 10,000 person-years). Also in that study, the hazard ratios (HRs) of AC for diabetic patients remained significantly higher than those for non-diabetic patients ($P<0.001$). Several studies have demonstrated that the hyperglycemia associated with DM can trigger collagen matrix changes within the joints [11,12]. These changes ultimately induce the fibrotic and inflammatory alterations associated with the histochemical status of the disease [3,13]. In addition, Esposito et al. [5] reported that hyperglycemia itself is a pro-inflammatory state.

The prevalence of DM in adults has increased worldwide over the past few decades [14]. The International Diabetes Federation (IDF) warns that the global number of diabetic patients will increase to 642 million by 2040, with an overall prevalence of 10.4% in the worldwide population [15]. DM can damage all organs of the body, including the musculoskeletal system, and can cause many health complications [16]. Thus, the increasing prevalence of DM could lead to a larger public health burden.

Considering the increasing prevalence of DM worldwide, this study aimed to analyze the relationship between the duration of type 2 diabetes mellitus (T2DM) and AC through a large-scale, nationwide, population-based cohort study conducted in the Republic of Korea. To the best of our knowledge, this study is the first nationwide population-based cohort study to demonstrate an association between T2DM (including prediabetes) and AC. We investigated the HRs and incidence rates (IRs) of AC in subjects with prediabetes and T2DM. Subjects with T2DM were subdivided into two groups according to their history of T2DM medication use to evaluate the influence of T2DM on the IRs and HRs of AC. We confirmed that the risk of AC differs by DM status, and compared the risk of AC between T2DM and non-T2DM populations.

METHODS

Data collection

This study used data from the Korean National Health Insurance Service (NHIS) Claims Database (in which diagnoses are recorded using International Classification of Diseases, Tenth Revision [ICD-10] codes), which contains all yearly claims data for the Korean NHIS program, the Korean Medical Aid program, and long-term care insurance. In the Republic of Korea, all citizens are mandatorily enrolled in the NHIS; thus, the system provides coverage for almost the entire Korean population. Therefore, the Korean NHIS database is considered to represent the entire Korean population and has been used in population-based studies.

NHIS enrollees underwent a medical examination including measurements of height, weight, blood pressure, and waist circumference, as well as laboratory tests such as fasting glucose, cholesterol, triglycerides, and serum creatinine. Data on past medical history and health-related behaviors such as smoking, alcohol intake, and physical activity were collected using standardized self-report questionnaires. Quality control procedures for laboratory tests were performed in accordance with the Korean Association of Laboratory Quality Control. This study was conducted according to the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of our institution (IRB No. SSU-202007-HR-236-01). Informed consent was waived by the board.

Study population

In this longitudinal, nationwide, population-based cohort study, all subjects who underwent an NHIS medical checkup between January 1, 2009 and December 31, 2009, were extracted from the medical checkup database. The date of the checkup was used as the baseline. The endpoint was new-onset AC during follow-up, which corresponded to when patients had visited the hospital or private clinic three times within 1 year and received a diagnostic code of AC (ICD-10 code, M750). Regular short-term follow-up is typical to assess the recovery of shoulder joint range of motion in the early phase of AC treatment. We excluded patients with ICD-10 code M750 who visited the hospital only once or twice, to reduce selection bias. We also excluded patients younger than 20 years ($n=4,481$), those with type 1 diabetes mellitus (T1DM) ($n=72,237$), those who had ever visited a hospital and received diagnostic code M750 at least once before January 2009 ($n=520,097$), and those with missing data ($n=131,886$). In addition, to prevent reverse causality, we excluded patients who had ever received diagnostic code M750 or died within 1 year of the date of medical evaluation provided by the Korean National Health Insurance Corporation (defined as 1 lag period; $n=38,376$). Finally, a total of 3,471,745 subjects were enrolled in the study (Fig. 1). The

study population was followed from baseline (date of NHIS medical checkup) until the endpoint (new-onset AC) or December 31, 2018 (whichever was first).

Definition of diabetes

DM status was determined based on laboratory test results from the NHIS medical checkup, and from the claims history for antidiabetic medications under ICD-10 code E11–14 before the checkup (from January 1, 2002, to the baseline). A fasting plasma glucose (FPG) level ≥126 mg/dL was defined as T2DM. The study population was initially divided into no-T2DM and yes-T2DM groups (Fig. 1). Subjects who had a FPG level <126 mg/dL and no claims history for antidiabetic medication were classified into the no-T2DM group, which was further divided into normal and prediabetes groups. The normal group included subjects with a FPG level <100 mg/dL. The prediabetes group included subjects with a FPG level of 100 to 126 mg/dL. The yes-T2DM group included subjects with a FPG level ≥126 mg/dL, as well as those with a claims history for antidiabetic medication regardless of FPG level. The yes-T2DM group was divided into new-onset T2DM and T2DM groups according to the claims history for antidiabetic medication. Subjects who had a FPG ≥126 mg/dL and no claims history for antidiabetic medication were assigned to the new-T2DM group. Subjects who had a claims history for antidiabetic medication were assigned to the T2DM group.

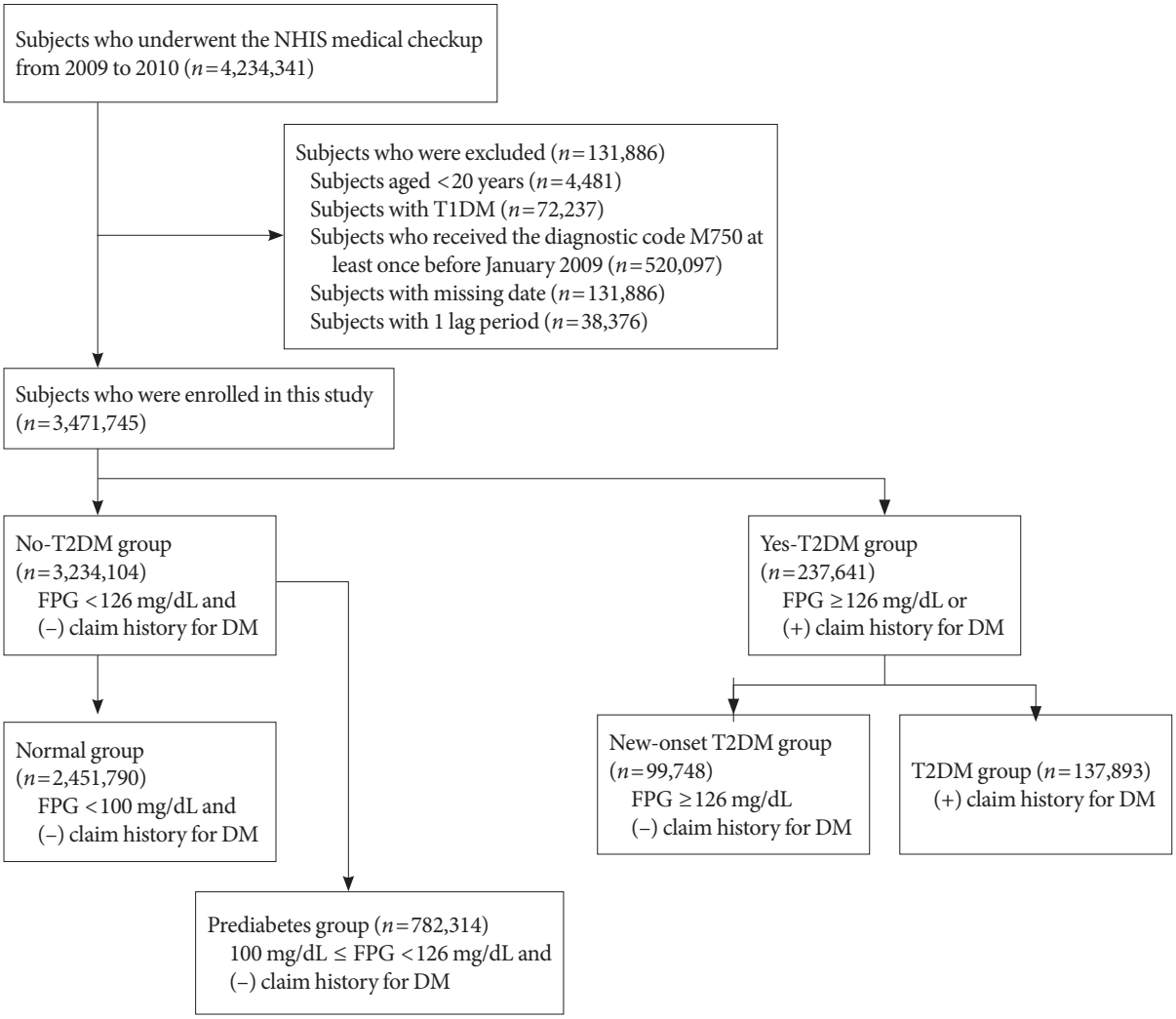

Fig. 1. Study design and patient characteristics. NHIS, National Health Insurance Service; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; DM, diabetes mellitus.

Statistical analysis

Patient baseline characteristics are presented as mean±standard deviation (SD) for continuous variables, and number and percentage for categorical variables. Normally distributed continuous variables are expressed as mean±SD and were investigated by analysis of variance. Categorical variables were examined using the chi-square test. Subjects were categorized into four groups according to the duration of T2DM. The IRs of AC were calculated by dividing the number of incident cases by the total follow-up duration and are expressed as the incidence of AC per 1,000 person-years. The association between the duration of T2DM and risk of AC was evaluated with Cox proportional hazard regression models. Model 2 was adjusted for age and sex, and model 3 for age, sex, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index (BMI). Results are presented as HRs with 95% confidence intervals (CIs) using the normal group as a reference. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and $P<0.05$ was considered to indicate significance.

RESULTS

Baseline characteristics

The analysis included 3,471,745 members of the general Korean population. During the mean follow-up of 7.9±1.54 years,

Table 1. Baseline characteristics of 3,471,745 participants with and without shoulder adhesive capsulitis

Variable	No adhesive capsulitis (*n*=3,178,557)	Adhesive capsulitis (*n*=293,188)	*P* value
Age, yr	44.29±13.48	53.17±10.89	<0.0001
Sex			<0.0001
Male	1,859,928 (58.51)	131,540 (44.87)	
Female	1,318,629 (41.49)	161,648 (55.13)	
Smoking			<0.0001
Non-smoker	1,794,567 (56.46)	196,072 (66.88)	
Former	462,988 (14.57)	42,341 (14.44)	
Current	921,002 (28.98)	54,775 (18.68)	
Alcohol drinking			<0.0001
Non-drinker	1,510,446 (47.52)	177,011 (60.37)	
Moderate	1,397,643 (43.97)	97,033 (33.1)	
Heavy	270,468 (8.51)	19,144 (6.53)	
Regular exercise	563,692 (17.73)	56,966 (19.43)	<0.0001
Body mass index, kg/m^2	23.61±3.54	23.99±3.05	<0.0001
Waist circumference, cm	563,692 (17.73)	56,966 (19.43)	<0.0001
Diabetes mellitus	202,102 (6.36)	35,539 (12.12)	<0.0001
Fasting glucose, mg/dL	95.71±21.5	100.3±26.49	<0.0001
Hypertension	728,296 (22.91)	100,025 (34.12)	<0.0001
Systolic blood pressure, mm Hg	121.83±14.81	123.31±15.36	<0.0001
Diastolic blood pressure, mm Hg	76.14±10.04	76.6±10.1	<0.0001
Dyslipidemia	495,888 (15.6)	69,033 (23.55)	<0.0001
Total cholesterol, mg/dL	194.05±40.97	199.23±42.27	<0.0001
HDL-C, mg/dL	56.54±32.34	56.48±35.33	0.4119
LDL-C, mg/dL	112.4±38.35	117.23±39.77	<0.0001
Triglycerides, mg/dL	111.09 (111.02–111.16)	115.75 (115.51–115.98)	<0.0001
Chronic kidney disease	194,911 (6.13)	21,640 (7.38)	<0.0001

Values are presented as mean±standard deviation, number (%), or median (range).
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

293,188 individuals (9.34%) had at least three hospital or private clinic visits, where they received the ICD-10 diagnostic code for AC (M750). Table 1 presents the baseline characteristics of the participants according to the presence of AC; those with AC were significantly older and had increased waist circumference, BMI, fasting glucose, systolic and diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol, and triglyceride values. Among the AC patients, there was also a higher proportion of females, and higher IRs of DM, hypertension, dyslipidemia, and chronic kidney disease (all $P<0.001$). Table 2 presents IRs and HRs of AC according to subgroup of T2DM and variables. Regardless of variables, IRs and HRs of AC increased with

Table 2. Incidence rates and hazard ratios of shoulder adhesive capsulitis according to subgroup of T2DM and variables

Variable		Groups	Total no.	No. of AC	Duration, yr[a]	IR[b]	HR (95% CI)	*P* value[c]
Age, yr	<40	Normal	1,029,752	18,454	8,491,683.04	2.1732	1 (ref)	<0.0001
		Prediabetes	208,096	4,714	1,710,618.73	2.7557	1.235 (1.195–1.276)	
		New-T2DM	18,353	650	149,686.15	4.3424	2.145 (1.992–2.310)	
		T2DM	6,343	543	50,607.7	10.7296	4.742 (4.376–5.138)	
	40–64	Normal	1,240,606	139,053	9,746,439.09	14.2671	1 (ref)	
		Prediabetes	485,035	55,367	3,782,314.25	14.6384	1.033 (1.022–1.043)	
		New-T2DM	66,733	8,714	510,089.15	17.0833	1.283 (1.256–1.310)	
		T2DM	89,217	16,813	656,365.04	25.6153	1.593 (1.567–1.619)	
	≥65	Normal	181,432	27,166	1,297,035.48	20.9447	1 (ref)	
		Prediabetes	89,183	12,895	633,229.26	20.3639	0.966 (0.946–0.987)	
		New-T2DM	14,662	1,984	100,135.33	19.8132	0.964 (0.922–1.008)	
		T2DM	42,333	6,835	285,434.07	23.9460	1.113 (1.085–1.143)	
Sex	Male	Normal	1,321,457	73,570	10,610,598.97	6.9336	1 (ref)	<0.0001
		Prediabetes	509,456	37,565	4,021,634.04	9.3407	1.105 (1.091–1.119)	
		New-T2DM	74,159	7,005	554,317.3	12.6372	1.412 (1.379–1.446)	
		T2DM	86,396	13,400	636,943.65	21.0380	1.642 (1.612–1.673)	
	Female	Normal	1,130,333	111,103	8,924,558.64	12.4491	1 (ref)	
		Prediabetes	272,858	35,411	2,104,528.21	16.8261	1.054 (1.042–1.067)	
		New-T2DM	25,589	4,343	205,593.33	21.1242	1.190 (1.156–1.225)	
		T2DM	51,497	10,791	355,463.16	30.3576	1.264 (1.239–1.289)	
Smoking	Non & Ex	Normal	1,782,564	152,645	14,139,350.41	10.7958	1 (ref)	<0.0001
		Prediabetes	547,672	58,153	4,259,071.37	13.6539	1.063 (1.053–1.074)	
		New-T2DM	62,083	8,343	479,294.21	17.4068	1.248 (1.221–1.275)	
		T2DM	103,649	19,272	741,035.69	26.0068	1.344 (1.324–1.365)	
	Current	Normal	669,226	32,028	5,395,807.2	5.9357	1 (ref)	
		Prediabetes	234,642	14,823	1,867,090.88	7.9391	1.133 (1.110–1.155)	
		New-T2DM	37,665	3,005	280,616.42	10.7086	1.520 (1.467–1.575)	
		T2DM	34,244	4,919	251,371.12	19.5687	1.966 (1.910–2.024)	
Body mass index, kg/cm^2	<25	Normal	1,771,104	129,267	14,139,536.9	9.1422	1 (ref)	<0.0001
		Prediabetes	468,651	42,144	3,665,002.85	11.4990	1.078 (1.066–1.090)	
		New-T2DM	51,147	6,143	379,368.43	16.1927	1.291 (1.258–1.325)	
		T2DM	69,253	12,748	504,933.85	25.2469	1.397 (1.371–1.424)	
	≥25	Normal	680,686	54,674	5,395,620.71	10.1330	1 (ref)	
		Prediabetes	313,663	29,056	2,461,159.4	11.8058	1.065 (1.049–1.080)	
		New-T2DM	48,601	6,178	380,542.2	16.2347	1.312 (1.278–1.347)	
		T2DM	68,640	12,978	487,472.96	26.6230	1.481 (1.452–1.510)	

(*Continued to the next page*)

duration of T2DM.

Overall IRs and HRs of AC according to the presence and duration of T2DM

Table 3 shows the IRs and HRs of AC according to the duration of T2DM. The IR of AC was 9.453 in the normal group, 11.912 in the prediabetes group, 14.933 in the new-T2DM group, and 24.3761 in the T2DM group. The HRs of AC was increased in the presence of T2DM. The HRs of AC after full adjustment for confounding variables (age, sex, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and BMI) was 1 in the normal group, 1.084 (95% CI, 1.075 to 1.094) in the prediabetes group, 1.312 (95% CI, 1.287 to 1.337) in the new-T2DM group, and 1.473 (95% CI, 1.452 to 1.494) in the T2DM group. The secular trend of the IRs and the HRs according to duration of T2DM was statistically significant ($P<0.0001$)

Table 2. Continued

Variable		Groups	Total no.	No. of AC	Duration, yr[a]	IR[b]	HR (95% CI)	*P* value[c]
Hypertension	No	Normal	2,007,131	134,315	16,308,121.56	8.2361	1 (ref)	<0.0001
		Prediabetes	531,543	44,242	4,309,247.63	10.2668	1.104 (1.093–1.116)	
		New-T2DM	56,829	5,542	435,235.47	12.7333	1.400 (1.366–1.436)	
		T2DM	47,921	9,064	405,142.69	22.3724	1.667 (1.633–1.701)	
	Yes	Normal	444,659	50,358	3,227,036.05	15.6050	1 (ref)	
		Prediabetes	250,771	28,734	1,816,914.62	15.8147	1.012 (0.996–1.027)	
		New-T2DM	42,919	5,806	324,675.16	17.8825	1.187 (1.155–1.220)	
		T2DM	89,972	15,127	587,264.12	25.7584	1.279 (1.255–1.302)	
Dyslipidemia	No	Normal	2,140,875	150,597	17,133,696	8.7895	1 (ref)	<0.0001
		Prediabetes	619,897	53,690	4,889,530.7	10.9806	1.087 (1.077–1.098)	
		New-T2DM	72,547	7,189	532,225.67	13.5074	1.324 (1.294–1.354)	
		T2DM	73,505	12,679	568,349.14	22.3085	1.469 (1.443–1.495)	
	Yes	Normal	310,915	34,076	2,401,461.61	14.1897	1 (ref)	
		Prediabetes	162,417	19,286	1,236,631.55	15.5956	1.038 (1.020–1.057)	
		New-T2DM	27,201	4,159	227,684.96	18.2665	1.269 (1.230–1.310)	
		T2DM	64,388	11,512	424,057.67	27.1473	1.399 (1.370–1.429)	

HR was adjusted for age, sex, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index.
T2DM, type 2 diabetes mellitus; AC, shoulder adhesive capsulitis; IR, incidence rate; HR, hazard ratio; CI, confidence interval; Non & Ex, non-smoker & ex-smoker.
[a]Duration, total follow-up period of all subjects, [b]Per 1,000 person-years, [c]*P* value for trend, according to Cox proportional hazard regression analyses.

Table 3. Incidence rates and hazard ratios of shoulder adhesive capsulitis according to T2DM status

Groups	Total no.	No. of AC	Duration, yr[a]	IR[b]	HR (95% CI)		
					Model 1	Model 2	Model 3
Normal	2,451,790	184,673	19,535,157.61	9.4534	1 (ref)	1 (ref)	1 (ref)
Prediabetes	782,314	72,976	6,126,162.25	11.9122	1.261 (1.25–1.272)	1.088 (1.079–1.098)	1.084 (1.075–1.094)
New-T2DM	99,748	11,348	759,910.63	14.9333	1.583 (1.553–1.613)	1.313 (1.288–1.339)	1.312 (1.287–1.337)
T2DM	137,893	24,191	992,406.81	24.3761	2.592 (2.558–2.627)	1.492 (1.472–1.513)	1.473 (1.452–1.494)
P value[c]					<0.0001	<0.0001	<0.0001

Model 1: unadjusted; Model 2: adjusted for age and sex; Model 3: adjusted for age, sex, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index.
T2DM, type 2 diabetes mellitus; AC, shoulder adhesive capsulitis; IR, incidence rate; HR, hazard ratio; CI, confidence interval.
[a]Duration, total follow-up period of all subjects, [b]Per 1,000 person-years, [c]*P* value for trend, according to Cox proportional hazard regression analyses.

(Fig. 2). Table 4 presents subgroup analysis of IRs and HRs of shoulder AC by age and sex according to presence of T2DM. Regardless of age and sex, presence of T2DM increased the HR of AC. Interestingly, the younger adult group (age 20–29 and 30–39 years) and male group showed higher HR of AC according to presence of T2DM compared to the older adult group

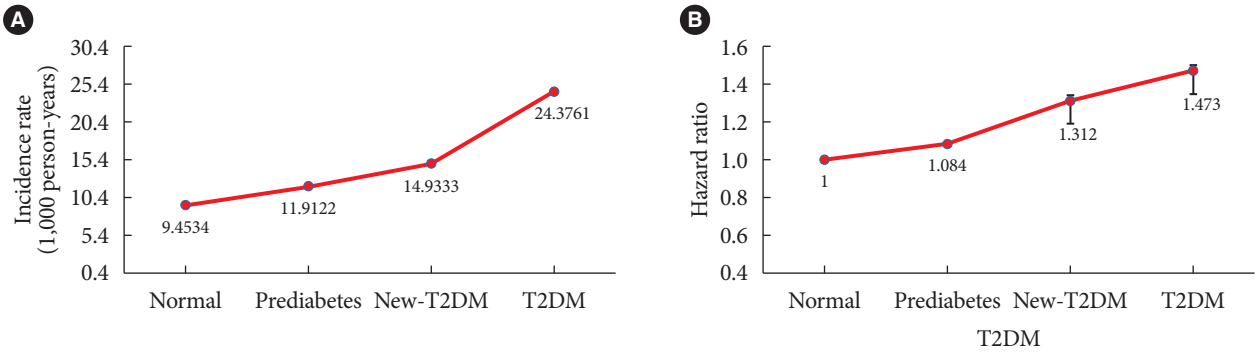

Fig. 2. (A) Incidence rate and (B) adjusted hazard ratio of shoulder adhesive capsulitis by duration of diabetes mellitus after adjusting for age, sex, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index. All *P* for interaction <0.001. T2DM, type 2 diabetes mellitus.

Table 4. Subgroup analysis of incidence rates and hazard ratios of shoulder adhesive capsulitis by age and sex according to presence of T2DM

	Groups	Total no.	No. of AC	Duration, yr[a]	IR[b]	HR (95% CI)	*P* value[c]
Age, yr							
20–29	T2DM (–)	495,995	3,757	4,106,251.64	0.9149	1 (ref)	<0.0001
	T2DM (+)	4,346	72	35,890.55	2.0061	2.509 (2.005–3.139)	
30–39	T2DM (–)	741,853	19,411	6,096,050.13	3.1842	1 (ref)	
	T2DM (+)	20,350	1,121	164,403.3	6.8186	2.401 (2.266–2.545)	
40–49	T2DM (–)	919,266	82,549	7,329,519.4	11.2625	1 (ref)	
	T2DM (+)	54,586	8,003	417,646.15	19.1622	1.806 (1.765–1.849)	
50–59	T2DM (–)	606,814	80,487	4,698,566.11	17.1301	1 (ref)	
	T2DM (+)	69,628	12,033	516,335.96	23.3046	1.430 (1.402–1.458)	
60–69	T2DM (–)	318,179	50,980	2,381,312.83	21.4084	1 (ref)	
	T2DM (+)	57,145	10,107	411,001.56	24.5911	1.169 (1.144–1.194)	
70–79	T2DM (–)	131,128	18,840	926,577.41	20.3329	1 (ref)	
	T2DM (+)	27,462	3,870	184,419.25	20.9848	1.033 (0.997–1.069)	
≥80	T2DM (–)	20,869	1,625	123,042.34	13.2068	1 (ref)	
	T2DM (+)	4,124	333	22,620.67	14.721	1.114 (0.990–1.254)	
Sex							<0.0001
Male	T2DM (–)	1,830,913	111,135	14,632,233.01	7.5952	1 (ref)	
	T2DM (+)	160,555	20,405	1,191,260.95	17.1289	1.511 (1.488–1.534)	
Female	T2DM (–)	1,403,191	146,514	11,029,086.85	13.2843	1 (ref)	
	T2DM (+)	77,086	15,134	561,056.49	26.9741	1.234 (1.213–1.255)	

HR was adjusted for age, sex, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index.
T2DM, type 2 diabetes mellitus; AC, shoulder adhesive capsulitis; IR, incidence rate; HR, hazard ratio; CI, confidence interval.
[a]Duration, total follow-up period of all subjects, [b]Per 1,000 person-years, [c]*P* value for trend, according to Cox proportional hazard regression analyses.

(age 40–49, 50–59, 60–69, 70–79, and ≥80 years) and the female group.

DISCUSSION

This large-scale, longitudinal, nationwide, population-based cohort study of 3,471,745 subjects demonstrated that the risk of AC increased in the prediabetes group and was associated with T2DM status. The IRs and HRs of AC increased with duration of T2DM regardless of variables. The IRs and HRs of AC were highest in the T2DM group, which included subjects who had a claims history for antidiabetic medication. In subgroup analysis, presence of T2DM increased the HR of AC regardless of age and sex. However, the younger adult group and male group showed higher HRs of AC according to presence of T2DM compared to the older adult group and the female group.

Among the components of metabolic syndrome, DM has been established as a risk factor for AC [2,9,17-21]. In one large-scale cohort study evaluating the risk of AC in a DM cohort, Lo et al. [9] reported that the incidence of AC was 3.08 times that of the comparison cohort (146.9 vs. 47.7 per 10,000 person-years). Also, the HRs of AC for diabetic patients remained significantly higher than that for non-diabetic participants ($P<0.001$). The prevalence of AC (12.4%) in their DM subjects is between those found in T1DM (10.3%) and T2DM (22.4%). However, their study included far fewer subjects than ours. A total of 5,109 DM cases and 20,473 reference patients were analyzed in their study, which did not exclude T1DM subjects.

The exact cause and pathology of AC is still unknown. Neviaser and Neviaser [2] reported that biopsies of the capsule showed a chronic absence of synovial lining, inflammatory infiltrate, and subsynovial fibrosis. They also found perivascular lymphocytic reactions. However, biopsy specimens from patients in the first stage of AC demonstrated a clear progression from perivascular mononuclear inflammatory infiltrates to reactive fibrosis of the capsule, which suggests an inflammatory origin [2,22]. Elevated levels of transforming growth factor-β and other profibrotic cytokines were present in capsular biopsy specimens and probably have the potential to trigger progression [23].

One hypothesis is that the hyperglycemia associated with DM can induce collagen changes within the joints [11,12]. These changes in the collagen matrix ultimately trigger the fibrotic and inflammatory alterations seen in pathologic and histochemical studies of the disease [3,13]. In addition, Esposito et al. [5] reported that hyperglycemia itself is a pro-inflammatory state. Several studies observed fibrosis induction via the proliferation of several cell types [24,25], as well as alterations in the quality and quantity of the extracellular matrix in a variety of DM patients' tissues [26]. Increased expression of vascular endothelial growth factor and angiogenesis in diabetes-associated AC has also been observed [27]. Previous reports also suggest an immunological pathogenesis of AC and DM [24,28-31]. It is possible that these two conditions are related.

To the best of our knowledge, this study is the first nationwide, population-based cohort study to investigate the link between T2DM status (including prediabetes) and AC. Our results revealed that prediabetes increases the risk of AC. Several studies showed that the duration of T2DM can affect the progression of diabetic osteopathy, and some studies reported a link between the duration of T2DM and fractures [32,33]. However, no study has reported an association between the duration of T2DM and AC. There were two case series studies which investigated the relationship between prediabetes and AC. Tighe and Oakley [7] reported that among 88 AC patients, the prevalence of DM in patients with AC was 38.6% (34 of 88) and that of prediabetes was 32.95% (29 of 88). Thus, they insisted that practitioners should consider the risk of DM and prediabetes in patients presenting with AC. On the other hand, another case series of 50 AC patients reported an opposite relationship between prediabetes and AC [34]. That study enrolled patients with a diagnosis of idiopathic AC and no known previous diagnosis of DM or prediabetic conditions. They underwent a 2-hour oral glucose tolerance test. Four patients with idiopathic frozen shoulder (8%) were found to be prediabetic and no patients were diabetic. All four patients reported a history of DM in their parents or siblings. The authors concluded that patients diagnosed with idiopathic AC shoulder who are 60 years or younger and are not known DM have a similar probability of having DM or prediabetes to an age-matched population. So they recommended no routine diabetic workup is warranted specifically for those patients. The major limitation of both studies was the small sample size. Therefore, the findings may not be generalizable to all populations.

This study had several important strengths. First, it was a large-scale, nationwide, population-based cohort study enrolling 3,471,745 normal, 782,314 prediabetic, and 237,641 diabetic subjects. This large number of subjects ensured sufficient

statistical power. Second, data from the NHIS, in which all citizens of the Republic of Korea are mandatorily enrolled, were analyzed, so there is little possibility of selection bias. Third, the prediabetes group was analyzed separately, where the association between prediabetes and AC has been rarely assessed.

There were several limitations to our study, such that the results should be interpreted with caution. First, our study only analyzed data from citizens of the Republic of Korea. Therefore, our results may not be generalizable to the worldwide population. Second, we used ICD-10 codes to identify patients with AC; therefore, patients who did not visit a hospital were not included in this study. Third, no information about shoulder range of motion was available, so we could not assess the association between diabetic status and AC severity. Fourth, we could not analyze the severity of T2DM, which can influence musculoskeletal health. Glycosylated hemoglobin (HbA1c), insulin use, and the type of antidiabetic medication were not considered in this study. Although, HbA1c of 5.7% to 6.4% is considered as prediabetes, we could not include these data. Fifth, comorbidities were not recorded. Despite adjusting for variables including hypertension, dyslipidemia, BMI, and health-related behaviors, various medical conditions could impact musculoskeletal health and the severity of T2DM such as steroid use, pancreatic disease, and other endocrinologic and rheumatologic diseases.

In summary, this large-scale, longitudinal, nationwide, population-based cohort study of 3,471,745 subjects demonstrated that the risk of AC increases in prediabetic patients and is associated with T2DM status. This finding suggests that promoting musculoskeletal health should be emphasized in prediabetic and diabetic patients care plans.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: J.H.K., H.S.K., K.H.
Acquisition, analysis, or interpretation of data: K.H., B.S.K.
Drafting the work or revising: J.H.K., H.S.K., K.H.
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FUNDING

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2021R1A2C2013890).

ACKNOWLEDGMENTS

None

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