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ORIGINAL ARTICLE

Low level of hemoglobin A1c and the increased incidence of herpes zoster: longitudinal study

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Abstract

Little is known about the association between glycemic status and herpes zoster. The aim of this study was to evaluate whether glycemic status, including both high and low hemoglobin A1c(HbA1c), is associated with subsequent herpes zoster. We conducted a retrospective longitudinal study in a large teaching hospital in Tokyo, Japan, from 2005 to 2016. We included all participants who underwent voluntary health check-ups at the hospital. Our primary outcome was the incidence of herpes zoster in groups of individuals stratified by HbA1c levels, which were compared using the generalized estimating equation (GEE), adjusting for participants' demographic characteristics, social history, body mass index, and comorbidities. A total of 81,466 participants were included in this study. The mean age (standard deviation) was 46.5 (12.1), and 39,643 (48.7%) participants were male. Among them, 1751 (2.1%) were diagnosed with diabetes prior to their first visits. After a median follow-up of 1784 [interquartile range (IQR), 749–3150] days, 673 (0.8%) participants developed herpes zoster. The incidence of herpes zoster was 1.45 per 1000 person-years. Compared with the reference group (HbA1c of 5.0–6.4%), the lowest HbA1c group (HbA1c of < 5.0%) had a significantly higher adjusted odds ratio (OR) (OR 1.63; 95% confidence interval (CI), 1.07–2.48) of developing herpes zoster. The group with an HbA1c of ≥ 9.5% had a higher but nonsignificant OR than the reference group (OR 2.15; 95% CI, 0.67–6.94). Our longitudinal study demonstrated that individuals in the lowest (< 5.0%) HbA1c group had a significantly higher risk of developing herpes zoster than the reference group (HbA1c of 5.0–6.4%) after adjusting for covariates.

Keywords Herpes zoster · Cancer · Hemoglobin A1c · Glycemic status · Longitudinal

Introduction

Diabetes is one of the most well-known and well-evaluated risk factors for infectious diseases [1, 2]. A previous matched cohort study in a primary care setting found that diabetic patients had 1.21 times higher adjusted odds for any infectious diseases than nondiabetic individuals [3]. Another retrospective cohort study showed that patients with type 1 diabetes had a 1.66 times higher incidence rate and those with type 2 diabetes had a 1.46 times higher incidence rate for any infectious disease and had 3.71 times and 1.88 times higher infection-related hospitalization rates than nondiabetic individuals, respectively [4].

Several explanations have been postulated for the association between diabetes and subsequent infectious diseases [5]. First, the immune response is impaired in hyperglycemia [6, 7]. Many immune responses, including cell-mediated immunity, are suppressed in diabetic patients with hyperglycemia. Immunocompromised patients with reduced cell-mediated immunity have an increased risk of reactivation of varicella-

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zoster virus, resulting in herpes zoster, and such immunocompromised patients include those with cancer [8], chronic hepatitis [9], chronic kidney disease [10], or autoimmune diseases [11].

However, the results have been different among reports, and it has not been determined whether diabetes is one of the risk factors for herpes zoster. A previous systematic review and meta-analysis reported that diabetic patients had a 1.30 times higher odds ratio for developing herpes zoster than non-diabetic patients [12]. Another large nationwide cohort study failed to show evidence of an increased risk for herpes zoster among diabetic patients [13]. In addition, there have been very few studies investigating the association between glycemic status and herpes zoster.

In addition to diabetes itself, poor glycemic control is currently considered a risk factor for infectious disease among diabetic patients [14]. Although poor glycemic control among diabetic patients has been extensively studied and was determined to be a factor that makes patients susceptible to infectious diseases, low glycemic status has never been evaluated as a risk factor for infectious diseases. From the clinical research perspective, interestingly, hemoglobin A1c (HbA1c) levels lower than 6.0% were associated with slightly higher hospitalization or death from infectious disease than HbA1c levels 6.0–7.0% among diabetic patients, although the difference was not statistically significant [14]. From a basic science research perspective, glycolysis is necessary for the activation of immune cells, suggesting that their activation is impaired in low glycemic status [15]. Thus, we postulated that low glycemic status was also associated with infectious diseases and aimed to elucidate this hypothesis in a large population by conducting this study to verify whether glycemic status, including both high and low HbA1c, is associated with the development subsequent herpes zoster.

Methods

We conducted a retrospective longitudinal study at St. Luke's International Hospital, a large teaching hospital in Tokyo, Japan, from 2005 to 2016. We included all participants who underwent voluntary health check-ups at the Department of Preventive Medicine in the hospital. We excluded participants who had a prior history of herpes zoster or who declared opt-out agreements for their anonymized data to be used in this research. Our primary outcome was the incidence of herpes zoster. We compared the outcome by HbA1c categories, adjusting for participants' demographic characteristics, social history, body mass index (BMI), and comorbidities.

This study was approved by the Ethical Committee Institutional Review Board at St Luke's International Hospital (17-R022: comprehensive approval).

Herpes zoster

Herpes zoster was clinically diagnosed by the physician who saw the patient based on dermatological findings and the presence of antigen titers against varicella-zoster virus. The diagnostic data were extracted from electronic medical records of the hospital based on the International Classification of Diseases (ICD)-10 [16]. We included development of herpes zoster based on ICD-10 diagnostic codes, which were coded by the physician, not based on laboratory-based diagnosis, such as antigen titers. If participants developed herpes zoster more than once during the study period, the first episode was used for analysis.

Hemoglobin A1c measures

HbA1c was measured in all participants as a part of the health check-up at baseline and at follow-up visits. HbA1c values measured by the Japanese Diabetes Society were converted into values by the National Glycohemoglobin Standardization Program [17]. HbA1c values were stratified into five groups, namely, < 5.0%, 5.0–6.4%, 6.5–7.9%, 8.0–9.4%, and ≥ 9.5%, considering the 5.0–6.4% group as a reference. The reason why we stratified our sample as above was following. First, we defined HbA1c of 6.5% (fasting blood glucose (FBG) of 126 mg/dl) as one of the cut-off values based on the World Health Organization (WHO) diabetes diagnostic criteria [18]. Although previous studies used the interval of 0.5% or 1.0% due to mainly focusing on either diabetic patients or nondiabetic people, our study, involved both, used the interval of 1.5% to divide our sample effectively. We defined the 5.0–6.4% group as a reference, because this group was highest HbA1c group within normal limit in our categorization. Repeatedly measured HbA1c values of each participant over time were considered time-dependent variables and incorporated in the longitudinal analysis.

Covariates

Because the incidence of herpes zoster is related to a variety of conditions, we included the following covariates as adjustment for multivariate analysis. Participants' demographics, including age and sex, were obtained. In terms of social history, alcohol consumption, smoking status, and exercise habits were obtained based on participants' self-reports. Alcohol consumption (abstainer, occasional drinker, regular drinker) and smoking status (never smoker, former smoker, current smoker) were categorized into three groups, and exercise habits were categorized into four groups (none, 1–2 times a week, 3–5 times a week, almost every day). Height and weight measured by a trained staff were used to calculate BMI, which was stratified into three groups: underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), and obesity/overweight (≥ 25.0 kg/

m^2) [19]. In terms of medical history, current history of diabetes and its pharmacological treatment status, cancer, chronic hepatitis/cirrhosis, hemodialysis, and autoimmune disease were obtained. These data were obtained at baseline and at each follow-up visit and were considered time-dependent variables.

Statistical methods

First, we compared the baseline characteristics of the individuals by five HbA1c groups using bivariate analyses. Then, longitudinal analyses were conducted with follow-up data. The generalized estimating equation (GEE) with binomial family, logit link, and unstructured correlation was applied to calculate the odds ratio (OR), adopting 5.0–6.4% of the HbA1c group as a reference. For multivariate analyses, different covariates were used for different models; model 1 included age, sex, and time variable for adjustments; model 2 added social histories, including alcohol consumption, smoking status, exercise habits, and BMI to model 1; model 3 added history of diabetes and its pharmacological treatment status to model 2; and model 4 added medical histories, including cancer, chronic hepatitis/cirrhosis, hemodialysis, and autoimmune disease. We conducted subanalyses by FBG category (each FBG was categorized into five groups, namely, < 100 mg/dl, 100–125 mg/dl, 126–199 mg/dl, 200–299 mg/dl, and ≥ 300 mg/dl, adopting 100–125 mg/dl group as a reference) to examine whether the results were observed only with HbA1c or whether they were consistent across glycemic measures. FBGs were also measured repeatedly at the same time to HbA1c and dealt as a time-dependent variable. For another subanalyses, we stratified participants by age (divided into two groups with the cut off of mean age of the samples) and sex. The interaction terms of age and sex between HbA1c group and development for herpes zoster were also examined. In addition, we conducted sensitivity analysis to compare the lowest HbA1c group (HbA1c of < 5.0%) with other groups with the data matching for baseline age and sex. The analysis was adjusted for same variables in model 4.

All analyses were performed by STATA 14 (STATA Corp., College Station, TX, USA) in 2019.

Results

Because 92 participants declared opt-out agreement and 182 had prior history of herpes zoster, a total of 81,466 participants were included in this study. The mean age (standard deviation) was 46.5 (12.1), and 39,643 (48.7%) participants were male. Among the participants, 1751 (2.1%) were diagnosed with diabetes prior to their first visits. Table 1 shows a comparison of the participants' characteristics categorized by five HbA1c categories. Participants who belonged to groups with low HbA1c levels tended to include more females and to be younger but less obese/overweight than participants in higher HbA1c groups. Red blood cell (RBC) values and indices, hemoglobin, hematocrit, mean cell volume (MCV), mean corpuscular hemoglobin (MCH), and mean cell hemoglobin concentration (MCHC) were clinically similar across the groups.

During a median follow-up of 1784 [interquartile range (IQR), 749–3150] days, 673 participants (0.8%) developed herpes zoster. The incidence rate of herpes zoster was 1.45 per 1000 person-years. Table 2 shows the results of the GEE from different models. Compared with the reference group (HbA1c of 5.0–6.4%), the lowest HbA1c group (HbA1c of < 5.0%) had a significantly higher adjusted OR (OR 1.63; 95% confidence interval [CI], 1.07–2.48 in model 4) of herpes zoster through all models. The group with HbA1c of ≥ 9.5% had higher but nonsignificant ORs than the reference group (OR 2.15; 95% CI, 0.67–6.94 in model 4). Other HbA1c groups had a similar risk of herpes zoster compared with the reference group (OR 1.06; 95% CI, 0.71–1.58 for the group with HbA1c of 6.5–7.9% in model 4; OR 0.90; 95% CI, 0.32–2.54 for the group with HbA1c of 8.0–9.4% in model 4).

The results from the subanalysis by FBS category are shown in Table 3. Although the ORs were not statistically significant, the lowest FBS group tended to have a high OR for the development of herpes zoster.

In terms of subanalyses stratified by age and sex, the interaction term of age was statistically significant ($p < 0.01$), but that of sex was not ($p = 0.77$). Table 4 showed the adjusted ORs for development of herpes zoster stratified by sex and gender. The lowest HbA1c group had higher, but not statistical ORs among both male and female. The group had statistically higher OR in the analysis with younger participants, but not in the analysis with older participants.

In our sensitivity analysis with the data matching for baseline age and sex, the lowest HbA1c group (HbA1c of < 5.0%) still had higher OR for the development of herpes zoster compared with matched samples from other groups. (OR 1.74; 95% CI, 1.05–2.86).

Discussion

Our longitudinal study demonstrated that individuals in the lowest HbA1c group (< 5.0%) had a significantly higher risk of developing herpes zoster than individuals in the reference group (HbA1c of 5.0–6.4%) after adjusting for demographic characteristics, BMI, social history, and comorbidities. Those with the highest HbA1c level (≥ 9.5%) also had high but not significant odds of developing subsequent herpes zoster. Subanalysis by FBS category showed that the lowest FBS group had a high OR of herpes zoster, although the difference was not statistically significant.

Table 1 Baseline participant's characteristics by hemoglobin A1c categories

	Baseline hemoglobin A1c category					
	< 5.0% (*n* = 4630)	5.0–6.4% (*n* = 74,033)	6.5–7.9% (*n* = 2119)	8.0–9.4% (*n* = 465)	≥ 9.5% (*n* = 219)	*p* value
Age, year, mean (SD)	39.7 (9.3)	46.4 (12.0)	59.2 (10.3)	57.6 (10.6)	52.2 (9.9)	< 0.01
Male, *n* (%)	1933 (41.8)	35,581 (48.1)	1578 (74.5)	370 (79.6)	181 (82.7)	< 0.01
Development for herpes zoster, *n* (%)	26 (0.6)	607 (0.8)	33 (1.6)	4 (0.8)	3 (1.4)	< 0.01
Follow-up periods, days, median (IQR)	1737.5 (741–3557)	1786 (749–3114)	1781 (747–3074)	1769 (850–3268)	1270 (631–2796)	< 0.01
Follow-up periods, person-years	26,042	399,752	11,385	2549	1037	< 0.01
Alcohol consumption, *n* (%)						< 0.01
Abstainer	1465 (31.6)	28,754 (38.8)	835 (39.4)	195 (41.9)	82 (37.4)	
Occasional	831 (18.0)	13,326 (18.0)	365 (17.2)	78 (16.8)	48 (21.9)	
Regular	2334 (50.4)	31,953 (43.2)	919 (43.4)	192 (41.3)	89 (40.6)	
Smoking status, *n* (%)						< 0.01
Never	2995 (64.7)	45,734 (61.8)	892 (42.1)	174 (37.4)	69 (31.5)	
Former	871 (18.8)	16,750 (22.6)	764 (36.1)	168 (36.1)	73 (33.3)	
Current	764 (16.5)	11,549 (15.6)	463 (21.9)	123 (26.5)	77 (35.2)	
Exercise habit, *n* (%)						< 0.01
Almost none	2034 (43.9)	27,748 (37.5)	573 (27.0)	143 (30.8)	97 (44.3)	
1–2 times a week	1716 (37.1)	27,648 (37.4)	741 (35.0)	153 (32.9)	72 (32.9)	
3–5 times a week	561 (12.1)	11,538 (15.6)	435 (20.5)	100 (21.5)	31 (14.2)	
Almost all days	319 (6.9)	7099 (9.6)	370 (17.5)	69 (14.8)	19 (8.7)	
Body mass index, *n* (%)						< 0.01
Underweight (< 18.5 kg/m^2)	577 (12.5)	7241 (9.8)	61 (2.9)	4 (0.9)	7 (3.2)	
Normal (18.5–24.9 kg/m^2)	3529 (76.2)	52,774 (71.3)	1147 (54.1)	223 (48.0)	98 (44.8)	
Obesity/overweight (25 ≤ kg/m^2)	524 (11.3)	14,018 (18.9)	911 (43.0)	238 (51.2)	114 (52.1)	
Comorbidities, *n* (%)						
Known diabetes	2 (0.1)	386 (0.5)	941 (44.4)	317 (68.2)	105 (48.0)	< 0.01
Medication for diabetes	2 (0.1)	168 (0.2)	658 (31.1)	258 (55.5)	80 (36.5)	< 0.01
Cancer	63 (1.4)	2192 (3.0)	107 (5.1)	11 (2.4)	4 (1.8)	< 0.01
Chronic hepatitis/Cirrhosis	40 (0.9)	364 (0.5)	14 (0.7)	5 (1.1)	0 (0.0)	< 0.01
Hemodialysis	3 (0.1)	31 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	0.27
Autoimmune disease	2 (0.1)	93 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	0.37
Laboratory measures, mean (SD)						
Systolic blood pressure (mmHg)	113.3 (15.3)	117.4 (16.8)	130.5 (18.6)	131.6 (17.5)	130.6 (19.5)	< 0.01
Diastolic blood pressure (mmHg)	69.7 (10.6)	72.3 (11.4)	79.7 (11.2)	80.5 (11.0)	81.6 (12.4)	< 0.01
Fasting blood glucose (mg/dl)	92.7 (7.4)	97.8 (9.2)	135.4 (21.1)	171.3 (34.4)	237.6 (49.1)	< 0.01
LDL cholesterol (mg/dl)	100.4 (26.7)	1116.6 (30.1)	124.6 (31.5)	124.7 (31.9)	130.8 (34.6)	< 0.01
HDL cholesterol (mg/dl)	65.3 (15.9)	63.0 (15.5)	54.5 (14.1)	52.1 (12.9)	51.2 (12.0)	< 0.01
Triglyceride (mg/dl)	80.1 (59.8)	96.9 (73.5)	142.0 (108.3)	166.6 (176.7)	202.8 (153.4)	< 0.01
Complete cell count, mean (SD)						
Red blood cell (10^6/μl)	4.4 (0.5)	4.5 (0.4)	4.6 (0.4)	4.7 (0.4)	5.0 (0.5)	< 0.01
Hemoglobin (g/dl)	13.9 (1.4)	13.8 (1.4)	14.3 (1.3)	14.7 (1.3)	15.3 (1.3)	< 0.01
Hematocrit (%)	40.5 (3.8)	40.7 (3.9)	42.0 (3.7)	42.9 (3.6)	44.5 (3.5)	< 0.01
MCV (fl)	92.0 (5.1)	90.7 (5.0)	91.3 (4.8)	91.0 (4.6)	89.9 (4.8)	< 0.01
MCH (pg)	31.5 (2.0)	30.8 (2.0)	31.1 (1.9)	31.2 (1.9)	30.9 (1.8)	< 0.01
MCHC (%)	34.3 (0.8)	33.9 (0.8)	34.1 (0.7)	34.2 (0.8)	34.4 (0.7)	< 0.01
Platelet (10^3/μl)	231.7 (50.1)	237.8 (51.1)	230.7 (52.8)	231.1 (56.2)	227.1 (50.1)	< 0.01
White blood cell (10^3/μl)	5.1 (1.3)	5.2 (1.4)	5.8 (1.5)	6.2 (1.6)	6.5 (2.0)	< 0.01
Neutrophils (%)	58.4 (8.7)	57.4 (8.4)	57.4 (8.4)	57.6 (8.6)	58.4 (8.4)	< 0.01

Table 1 (continued)

	Baseline hemoglobin A1c category					
	< 5.0% (*n* = 4630)	5.0–6.4% (*n* = 74,033)	6.5–7.9% (*n* = 2119)	8.0–9.4% (*n* = 465)	≥ 9.5% (*n* = 219)	*p* value
Lymphocyte (%)	31.2 (7.6)	32.4 (7.7)	32.4 (7.8)	32.2 (7.9)	31.7 (8.0)	< 0.01
Monocyte (%)	6.5 (1.8)	6.3 (1.8)	6.5 (1.7)	6.5 (1.6)	6.3 (1.7)	< 0.01
Eosinophils (%)	3.1 (2.5)	3.1 (2.4)	3.0 (2.3)	3.0 (2.1)	3.0 (3.2)	0.57
Basophils (%)	0.7 (0.4)	0.7 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	< 0.01

We hypothesized that two main potential reasons may be related to the findings. First, the lowest glycemic status was independently associated with a high incidence of herpes zoster. Many previous studies have provided evidence that acute diseases, including infectious disease, cause hyperglycemia [20–22], or sometimes hypoglycemia [23, 24]. The mechanisms underlying the development of hypoglycemia induced by infectious diseases were considered to include increased glucose utilization in some tissues [25], decreased glucose production in the liver [26, 27], or adrenal insufficiency [28]. However, to the best of our knowledge, the reverse causation that low glycemic status itself is the risk factor for infectious diseases has never been reported. Previous research has shown that glycolysis is required for the activation and proliferation of effector T cells [29], which are mainly responsible for cell-mediated immunity. A clinical study found that cell-mediated immunity had more important roles than humoral immunity in the development herpes zoster [30]. Thus, low glycemic status may be associated with subsequent herpes zoster through the suppression of effector T cells.

Several hematological conditions lead to low HbA1c levels in nonanemic individuals, namely, minor thalassemia, Hb variants, and compensated hemolysis. Thalassemia patients are known to have immune deficiency mainly associated with iron overload [31]. Iron overload in thalassemia patients results not only from multiple blood transfusions but also from the premature death of RBCs in the bone marrow, ineffective erythropoiesis, and increased intestinal iron absorption; thus, nonanemic patients with minor thalassemia can have immune-related abnormalities that may contribute to the development of herpes zoster. A variety of Hb variants are associated with low HbA1c levels, and approximately one of three thousand Japanese people has a Hb variant, 70% of which are silent [32]. Although direct evidence that Hb variants are related to a susceptibility to infection is lacking, it is possible that a considerable number of individuals with Hb variants have compensated hemolysis and deranged iron metabolism, as in thalassemia patients, leading to immune deficiency. Similarly, compensated hemolysis associated with hereditary disorders of RBC enzymes or membranes and with other hemolytic anemias may affect the immune system. However, these mechanisms are just speculations at present, and detailed studies of the hematological characteristics of patients with low HbA1c levels who developed herpes zoster are obviously needed.

Vaccination against herpes zoster for patients with low HbA1c levels should be considered. Currently, it is recommended that people who are 50 years or older get vaccinated to prevent herpes zoster [33]. Additional indications are given to offering the vaccine to immunocompromised patients, especially for those who have received moderate to strong immunosuppressants [34, 35]. Our results indicated that individuals with low HbA1c but who are not otherwise

Table 2 The odds ratio for developing herpes zoster by following hemoglobin A1c categories from the generalized estimating equation

Odds ratio (95% confidence interval)					
Hemoglobin A1c	< 5.0%	5.0–6.4%	6.5–7.9%	8.0–9.4%	≥ 9.5%
Model 1	*1.62 (1.06–2.47)*	Reference	1.35 (0.97–1.89)	1.21 (0.45–3.26)	2.85 (0.91–8.90)
Model 2	*1.65 (1.08–2.52)*	Reference	1.31 (0.94–1.84)	1.20 (0.45–3.23)	2.75 (0.88–8.61)
Model 3	*1.65 (1.08–2.52)*	Reference	1.07 (0.72–1.59)	0.91 (0.32–2.54)	2.15 (0.67–6.95)
Model 4	*1.63 (1.07–2.48)*	Reference	1.06 (0.71–1.58)	0.90 (0.32–2.54)	2.15 (0.67–6.94)

Model 1 included age, sex, and time variables for adjustments. Model 2 added social histories, including alcohol consumption, smoking status and exercise habits, and body mass index to model 1. Model 3 added a diagnosis of diabetes and its treatment status to model 2. Model 4 added medical histories, including cancer, chronic liver disease/cirrhosis, chronic kidney disease, and collagen disease

The numbers in italics represent that its *p* value is less than 0.05

Table 3 The odds ratio for developing herpes zoster by following fasting blood glucose categories from the generalized estimating equation

Odds ratio (95% confidence interval)

Fasting blood glucose	< 100 mg/dl (no. of measures, 288,161)	100–125 mg/dl (no. of measures, 178,560)	126–199 mg/dl (no. of measures, 17,385)	200–299 mg/dl (no. of measures, 1271)	≥ 300 mg/dl (no. of measures, 106)
Model 1	*1.24 (1.04–1.47)*	Reference	*1.45 (1.01–2.06)*	1.44 (0.36–5.79)	—*
Model 2	1.17 (0.98–1.39)	Reference	1.42 (0.99–2.02)	1.40 (0.35–5.66)	—*
Model 3	1.19 (0.99–1.42)	Reference	1.14 (0.76–1.72)	1.07 (0.26–4.43)	—*
Model 4	1.19 (0.99–1.42)	Reference	1.14 (0.76–1.72)	1.07 (0.26–4.44)	—*

Model 1 included age, sex, and time variables for adjustments. Model 2 added social histories, including alcohol consumption, smoking status and exercise habits, and body mass index to model 1. Model 3 added a diagnosis of diabetes and its treatment status to model 2. Model 4 added medical histories, including cancer, chronic liver disease/cirrhosis, chronic kidney disease, and collagen disease

The numbers in italics represent that its p value is less than 0.05

*There was no development of herpes zoster in participants with a fasting blood glucose of 300 mg/dl or greater

immunocompromised might also be good candidates for vaccination to prevent future herpes zoster and post-herpetic neuralgia.

The reason why HbA1c levels ≥ 9.5% had a high odds ratio, albeit not statistically significant, for the incidence of herpes zoster was considered to be a lack of power. In fact, only three participants developed herpes zoster in the group with HbA1c levels ≥ 9.5% at baseline.

Our study had some limitations. First, our data did not include information about the vaccination received for herpes zoster, which may affect the outcome. However, as the herpes zoster vaccine was approved in 2016 in Japan and only a limited number of individuals would have been vaccinated, the effect of the vaccination on the results of the present study would be limited. Another limitation was that not all patients with herpes zoster visited our hospital, and it is likely that individuals who developed herpes zoster were diagnosed in other institutions, such as local clinics, and that their histories of herpes zoster were missing from our medical records. Therefore, the incident rates observed in this study (2.07 per 1000, including recurrent episode of herpes zoster) were slightly lower than those in the general population in Japan (4.15 per 1000, including recurrent herpes zoster) [36]. In addition to lost followed-up participants, our study design which excluded participant with prior history of herpes zoster contributed the reason for the lower incidence, because prior history could be a risk factor for herpes zoster.

Conclusion

Our longitudinal study demonstrated that individuals in the lowest (< 5.0%) HbA1c group had a significantly higher risk of developing herpes zoster than individuals in the reference group (HbA1c of 5.0–6.4%) after adjusting for demographic characteristics, BMI, social history, and comorbidities.

Compliance with ethical standards This study was approved by the Ethical Committee Institutional Review Board at St Luke's International Hospital (17-R022: comprehensive approval).

Table 4 The odds ratio for developing herpes zoster by following hemoglobin A1c categories from the generalized estimating equation, stratifying by sex or age

Odds ratio (95% confidence interval)

Hemoglobin A1c	< 5.0%	5.0–6.4%	6.5–7.9%	8.0–9.4%	≥ 9.5%
Stratified by gender					
Male (262 developed herpes zoster)	1.62 (0.79–3.30)	Reference	0.89 (0.52–1.53)	0.93 (0.28–3.15)	1.05 (0.14–7.78)
Female (411 developed herpes zoster)	1.64 (0.97–2.78)	Reference	1.30 (0.72–2.34)	0.76 (0.10 –5.73)	*4.61 (1.06–20.1)*
Stratified by age					
Younger than 47 years (265 developed herpes zoster)	*1.85 (1.16–2.93)*	Reference	0.30 (0.03–2.63)	1.49 (0.16–14.2)	—*
47 years or older (408 developed herpes zoster)	0.76 (0.24–2.38)	Reference	1.17 (0.77–1.77)	0.80 (0.24–2.62)	3.07 (0.94–10.0)

The model was adjusted for age (only the model stratifying by sex), sex (only the model stratifying by age), time variables, social histories, diagnosis of diabetes and its treatment status, and medical histories

*There was no development for herpes zoster among younger participants with HbA1c of 9.5% or higher

The numbers in italics represent that its p value is less than 0.05

Conflict of interest The authors declare that they have no conflict of interest.

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