Journal of the Formosan Medical Association (2016) 115, 343–349

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

The impact of ambient temperature on HbA1c in Taiwanese type 2 diabetic patients: The most vulnerable subgroup

Kai-Jen Tien [a,b], Chwen-Yi Yang [a], Shih-Feng Weng [c,d], Su-Yen Liu [e], Ming-Chia Hsieh [f,g], Chien-Wen Chou [a,*]

[a] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan*
[b] *Department of Senior Citizen Service Management, Chia Nan University of Pharmacy and Science, Tainan, Taiwan*
[c] *Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan*
[d] *Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan*
[e] *Department of Nursing, Chi Mei Medical Center, Tainan, Taiwan*
[f] *Division of Endocrinology and Metabolism, Department of Internal Medicine, Changhua Christian Hospital, Changhua, Taiwan*
[g] *Graduate Institute of Integrated Medicine, China Medical University, Taiwan*

Received 3 July 2014; received in revised form 16 March 2015; accepted 17 March 2015

KEYWORDS
HbA1c;
Taiwanese;
temperature;
type 2 diabetes

Background/Purpose: The relationship between temperature variability and HbA1c has been reported in Caucasians, but not for Asians of Taiwanese origin. This study investigated the impact of temperature on HbA1c in various groups of Taiwanese with type 2 diabetes in Taiwan.
Methods: For this longitudinal follow-up study which started in 2006, we recruited a total of 4399 patients with type 2 diabetes who had been regularly followed up at Chi Mei Medical Center and obtained local temperature data for 2006 to 2011 from Taiwan's Central Weather Bureau. We used a generalized estimated equation (GEE) to analyze the HbA1c level and its change over time with temperature and temperature changes, respectively.
Results: We found a negative correlation between HbA1c and temperature ($R = -0.475$, $p = 0.001$). For every 1°C decrement in temperature, there was an increase in the risk of having a HbA1c level >7% [$p < 0.001$, adjusted odds ratio (OR): 1.01]. There was a significantly higher risk of HbA1c > 7% among those in the lowest quartile of temperatures than the highest

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

* Corresponding author. Division of Endocrinology and Metabolism, Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan.
E-mail address: cacmmc@gmail.com (C.-W. Chou).

http://dx.doi.org/10.1016/j.jfma.2015.03.010

quartile ($p = 0.0038$, adjusted OR: 1.13). Patients with diabetic patients were at higher risk of HbA1C > 7% in the winter and spring than those in the summer (adjusted OR: 1.13, $p = 0.0027$; adjusted OR: 1.14, $p = 0.0022$). After adjusting for various confounders, we found people who were younger than 65 years old, people who had diabetes for longer than 6 years, and people who had a body mass index (BMI) < 24 to be more susceptible to temperature changes ($p = 0.0022$, β: 0.0095; $p < 0.0001$, β: 0.0125; $p < 0.0001$, β: 0.016, respectively).
Conclusion: Our study suggests cold weather may adversely affect HbA1c levels in Taiwanese people with type 2 diabetes, especially in people under 65 years old, people with diabetes for longer than 6 years, and those with a BMI < 24.

Introduction

The glycated hemoglobin A1c (HbA1c) level, a calculation of average glycemia over several months, is often used as a primary target in the treatment of diabetes. The American Diabetes Association (ADA) recommends that it should be calculated approximately every 3 months to determine whether a patient has reached and maintained this glycemic goal.[1] This goal may be important because the UK Prospective Diabetes Study (UKPDS) found a 14%, 37%, and 21% reduction in myocardial infarction, microvascular complications, and diabetes-related death for each 1% reduction in HbA1c.[2] However, a lower HbA1c level may not bring cardiovascular (CV) benefit. Intensive glycemic control has been found to show no significant reductions in CV outcomes in Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and the Veterans Affairs Diabetes Trial (VADT).[3,4] In fact, intensive glycemic control with a target A1C of <6% increased mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[5] Hence, it should be mentioned that glycemic goals be individualized and achieved safely in the ADA position statement.[6]

Fluctuations of HbA1c have been associated with seasonal change[7–9] as well as some physiological endocrine factors, environmental factors and social events.[10–12] Caney et al reported HbA1c levels in women with type 2 diabetes were susceptible to temperature.[13] A study of type 1 diabetes, found a correlation between temperature and HbA1c in schoolchildren, but not preschoolers.[14] In our daily clinical experience, some groups appear to be more vulnerable to temperature variation than others. However, few studies focus on the risk that temperature may pose to different subgroups. The studies that have focused on this topic have been conducted in Caucasian populations,[9,15,16] and most are either cross-sectional in design or have small sample sizes.[13,16] Cross-sectional studies, in particular, may produce biased results when applied to changes that occur over time.

Therefore, this investigation used a follow-up study design to observe HbA1c changes and temperature changes over a period of 5 years (from Jan 2006 to Jan 2011) in 4399 Taiwanese patients with type 2 diabetes and subgroups of this population in Taiwan.

Materials and methods

This observational follow-up study enrolled 4399 type 2 diabetic patients recruited from the diabetic clinic in the Metabolism Division at Chi Mei Medical Center in Tainan, a city located near the southwest coast of Taiwan. At enrollment in Jan 2006, all patients had been regularly followed up at least 6 months. Regular follow-ups were also performed for these patients during the study period which ended Jan 2011. All the patients participated in a comprehensive diabetes care program.[17] Physicians, diabetes educators, and dietitians cooperate to provide integrated and comprehensive care for each patient at every quarterly outpatient department visit. Data on sex, age, date of diagnosis of diabetes, and biophysical measurements such as triglyceride (TG), total cholesterol (TC), high density lipoprotein and low density lipoprotein cholesterol (HDL-C and LDL-C), blood pressure (BP) and body mass index (BMI) for each patient were collected for each patient at baseline and at 1 year. HbA1c, creatinine, and estimated glomerular-filtration rate (eGFR) were checked and recorded at baseline and every 3 months. The eGFR was calculated using the equation recommended by the National Kidney Foundation in the Modified Diet in Renal Disease. All antihypertensive, glucose-lowering, and lipid-lowering medications were also recorded every 3 months. Local temperature data from 2005 to 2011 were obtained from Taiwan's Central Weather Bureau (http://www.cwb.gov.tw/V7e/climate/monthlyData/mD.htm).

Statistical analyses

All values were reported as means ± SD or median with interquartile ranges or percentages. Because the distribution of TG was highly skewed, the variable was natural log transformed for all other analyses. We analyzed the odds ratio (OR) for HbA1C > 7% for seasons as categorical variables. We classified December to February as winter, March to May as spring, June to August as summer, and September to November as fall/autumn. Categorical cut-off points for

temperature were analyzed into quartiles. Because the study variables were recorded more than once during this study, the OR of HbA1c >7% for temperature as continuous or categorical variables (quartile as cut points: <21.8°C, 21.8°C ~26.3°C, 26.3°C ~28.4°C, >28.4°C) was obtained by logistic regression using the generalized estimated equation (GEE) method clustering each patient in this longitudinal data. The correlation matrix was set as exchangeable. GEE is often used to analyze longitudinal and other correlated response data, particularly if responses are binary. We calculated all the HbA1C changes for each person and the temperature changes during the study period in the GEE model.

This model helped control for those repeated variables rather than just using their values from baseline. We also adjusted the model for known confounders: age, sex, diabetes duration, BMI, eGFR, smoking, and use of lipid-lowering, antihypertension and glucose-lowering drugs.

A mixed effects model was used to define at-risk subgroups [male, female, age $\leq$ 65, age > 65, DM duration $\leq$ 6 years, DM duration > 6 years, BMI <24, 24 $\leq$ BMI $\leq$ 27, BMI > 27, eGFR$\leq$ 60, eGFR > 60, only diet control, only oral antidiabetes drugs (OAD), only insulin, and OAD + insulin] when the dependent variable HbA1C was treated as a continuous outcome. In this method, a random intercept is fitted for each patient and the weighted effect of repeated measurements was taken into account. The three models demonstrated the change of HbA1c for every 1°C decrement in temperature. Model 1 was an unadjusted model, Model 2 was adjusted for age, sex, diabetes duration, BMI, eGFR and smoking status, and Model 3 was adjusted for the same adjusted variables of model 2 plus use of lipid-lowering, antihypertension, and glucose-lowering drugs. Afterwards, Pearson's correlation coefficient was performed to address the relationship of mean HbA1c of each patient and temperature. All statistical tests were two-sided. A p value of <0.05 was considered significant.

Results

As can be seen in Table 1, a summary of the clinical characteristics of the patients, two-thirds of the 4399 type 2 diabetic patients we studied were followed up for at least 1 year. The mean follow-up period was 24.7 months. In total, 21,279 measurements of HbA1C were recorded during the study period. During this time, there were improvements in nearly all biophysical parameters, especially HbA1c and LDL cholesterol, as they were the focus of treatment.

As shown in Fig. 1, a depiction of the relationship between the temperature and HbA1c levels, we found a strong negative correlation between HbA1c and temperature ($R = -0.475$, $p = 0.001$).The lower the temperature, the higher the HbA1c.

We further categorized temperature as continuous or categorical variables to analyze the ORs of HbA1c > 7% (Table 2). Every 1°C decrement in temperature increased the risk of HbA1c > 7% (OR: 1.01, 95% CI: 1.01—1.02, $p < 0.001$). After adjusting for confounding factors (age, sex, diabetes duration, BMI, eGFR, smoking, use of lipid-lowering, antihypertension and glucose-lowering drugs), the risk remained significantly higher (OR: 1.01, 95% CI: 1.01—1.02, $p < 0.001$). We divided the temperatures into quartiles in the categorical analysis and used those in the highest quartile as the reference group. The group belonging to the lowest quartile were found to be at higher risk of HbA1c > 7% than the group belonging to the highest quartile in both unadjusted and adjusted models (OR: 1.12, 95% CI: 1.06—1.19, $p < 0.001$ and OR: 1.13, 95% CI: 1.04—1.22, $p = 0.0038$). Table 3 showed that diabetic

Table 1 The clinical characteristics of the patients and biophysical measurements at baseline and final visit.

Total numbers	4399	
Follow up 0.5~1 year	1414(32.14%)	
Follow up 1~3 year	1801(40.94%)	
Follow up 3~5 year	1184(26.92%)	
Mean follow-up years	2.06 ± 1.29	
DM duration (y)	7.94 ± 7.04	
Sex (Male/Female)	2194/2205	
Age (y)	62.05 ± 12.44	
Smoking (yes/no)	723/3676	
Biophysical data	Baseline	Last
SBP (mmHg)	136.88 ± 19.56	136.71 ± 19.30
DBP (mmHg)	79.70 ± 11.64	77.89 ± 11.12
BMI (kg/m^2)	25.69 ± 4.11	25.71 ± 4.09
AC sugar	152.02 ± 53.87	141.91 ± 50.65
Hb A1C (%)	8.17 ± 1.82	7.80 ± 1.52
CHOL (mg/dL)	193.86 ± 42.62	169.74 ± 38.84
TG (mg/dL)	151.07 ± 117.24	136.12 ± 103.72
Ln (TG) (mg/dL)	4.84 ± 0.57	4.74 ± 0.55
HDL-C (mg/dL)	52.99 ± 13.90	51.48 ± 13.75
LDL-C (mg/dL)	121.91 ± 38.43	99.93 ± 33.08
Creatinine (mg/dL)	1.07 ± 0.47	1.17 ± 0.75
eGFR (mL/min per 1.73 m^2)	63.97 ± 21.67	61.78 ± 23.26
Use of antihypertensive treatment (%)		
ACEI	307(6.98%)	316(7.18%)
ARB	895(20.35%)	875(19.89%)
CCB	1052(23.91%)	1084(24.64%)
Diuretics	255(5.80%)	235(5.34%)
β-blocker	319(7.25%)	333(7.57%)
Use of lipid-lowering medications (%)		
Statin	1382(31.42%)	1390(31.60%)
Fibrates	502(11.41%)	473(10.75%)
Statin + fibrates	81(1.84%)	96(2.18%)
None	2434(55.33%)	2440(55.47%)
Use of glucose-lowering treatment (%)		
Diet only	120(2.73%)	99(2.25%)
OAD therapy only		
Monotherapy	917(20.85%)	877(19.94%)
Two combinations	1819(41.35%)	1847(41.99%)
Three combinations	816(18.55%)	824(18.73%)
Insulin therapy only	278(6.32%)	277(6.30%)
OAD puls insulin	449(10.21%)	475(10.80%)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BMI = body mass index; CCB = calcium channel blocker; DBP = diastolic blood pressure; FPG = fasting plasma glucose; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; OAD = oral antidiabetes drugs; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride.

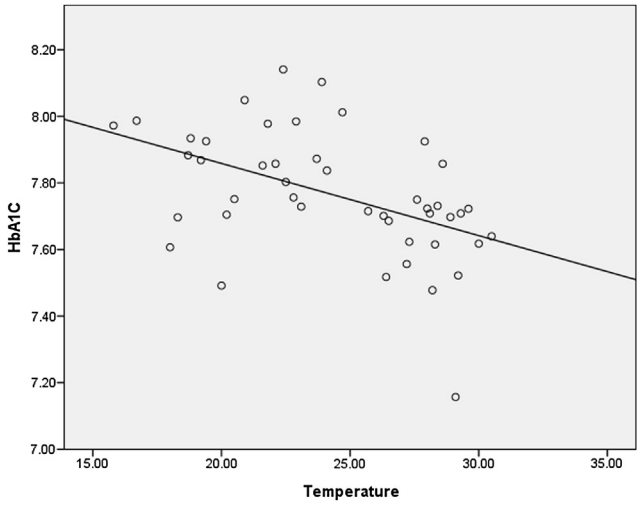

Figure 1 Correlation of HbA1c levels (%) and temperature (°C) (R = −0.475, p = 0.001).

patients were at higher risk of worsened glycemic control (HbA1C > 7%) in the winter and spring than those in the summer (adjusted OR: 1.13(1.04−1.22), $p = 0.0027$; adjusted OR: 1.14(1.05−1.25), $p = 0.0022$, respectively).

Table 4 shows the changes in HbA1c analyzed by every 1°C decrement in temperature. We classified the clinical phenotype of the population to determine which risk subgroups may be prone to these effects. Almost all phenotypes were influenced by temperature; both men and women were significantly influenced by temperature in both the unadjusted and adjusted models. In patients with age ≤65, every 1°C decrement in temperature significantly was associated with a 0.0095 unit increment in HbA1C, but not in those with age >65. Temperature changes also had a greater impact on patients who had diabetes for more than 6 years than for those who had it for 6 years or less (adjusted β: 0.0125, $p < 0.0001$; adjusted β: 0.0013, $p = 0.7076$, respectively). We found similar changes in those with BMI <24, but not in those with BMI 24−27 and >27. On average, there was a 0.016 unit increment in HbA1c level in those with BMI <24.

Discussion

Although there were many studies investigating the epidemiology and treatment of diabetes in Taiwan, the impact of ambient temperature on glycemic control was rarely discussed.[18−21] To our knowledge, this is the first 5-year observational study investigating the association between the temperature and HbA1c in patients with type 2 diabetes in Taiwan. We found a negative correlation between HbA1c and temperature: the lower the temperature, the poorer the glycemic control. The patients belonging to the lowest quartile of temperature had a 13% higher risk for HbA1c > 7%, compared with those belonging to the highest quartile. Although nearly all the tested subgroups are affected by the temperature, patients aged <65 years, those with diabetes longer than 6 years, and those with BMI <24 were more likely to be influenced by the temperature changes after adjusting for potential confounders.

Our findings demonstrate a seasonal variation in HbA1c levels. The risk of having a HbA1c > 7% was higher in those in the lowest quartile of temperatures than the highest. Most of the previous investigations were cross-sectional in design, had a small number of subjects, and had subjects of different ethnicities.[8,14,22,23] Our study was a 5-year follow-up study. In a cross-sectional study design, the HbA1c used for analysis was calculated from the mean HbA1c level in this population and so it is difficult to see the real impact of temperature on an individual patient. Some patients have been found to have seasonal HbA1c fluctuations and some patients show a reverse pattern of HbA1c fluctuations.[24] There are some plausible explanations for temperature associated changes in HbA1c in our study. Ishii et al[8] reported an increase in dietary intake and decrease in

Table 2 Odds ratios for HbA1C > 7% for temperature as continuous or categorical variables.

	Interpretation	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Continuous	Every 1°C decrement	1.01 (1.01−1.02)	<0.001	1.01 (1.01−1.02)	<0.001
Categorical	<21.8	1.12 (1.06−1.19)	<0.001	1.13 (1.04−1.22)	0.0038
	21.8∼26.3	1.10 (1.04−1.17)	0.0011	1.09 (1.00−1.18)	0.0459
	26.3∼28.4	1.00 (0.94−1.07)	0.9371	0.99 (0.92−1.08)	0.9234
	>28.4	Reference		Reference	

Adjust for age, sex, diabetes duration, BMI, eGFR, smoking, use of lipid-lowering, antihypertension, and glucose-lowering drugs.

Table 3 Odds ratios for HbA1C>7% for seasons as categorical variables.

	Interpretation	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Categorical	Spring	1.13 (1.07−1.20)	<0.0001	1.14 (1.05−1.25)	0.0022
	Summer	Reference		Reference	
	Fall	1.01 (0.96−1.06)	0.7574	0.98 (0.91−1.06)	0.5931
	Winter	1.12 (1.06−1.19)	<0.0001	1.13 (1.04−1.22)	0.0027

Adjust for age, sex, diabetes duration, BMI, eGFR, smoking, use of lipid-lowering, antihypertension, and glucose-lowering drugs.

Table 4 Unadjusted and adjusted model between HbA1c and temperature in subgroup analysis (every 1°C decrement).

Subgroup	Model 1 (unadjusted)		Model 2 (adjusted)		Model 3 (adjusted)	
	Estimate of HbA1c β(95% CI)	*p*	Estimate of HbA1c β(95% CI)	*p*	Estimate of HbA1c β(95% CI)	*p*
Sex						
Male	0.0111 (0.0058—0.00164)	<0.0001	0.0082 (0.0014—0.0150)	0.0182	0.0084 (0.0016—0.0151)	0.0157
Female	0.0087 (0.0041—0.0132)	0.0002	0.0063 (0.0003—0.0122)	0.0386	0.0061 (0.0002—0.0120)	0.0437
Age						
≤65	0.0116 (0.0069—0.0164)	<0.0001	0.0094 (0.0033—0.0155)	0.0025	0.0095 (0.0034—0.0156)	0.0022
>65	0.0073 (0.0022—0.0123)	0.0048	0.0041 (0.0254—0.0106)	0.2285	0.0042 (0.0024—0.0108)	0.2087
Diabetes duration						
≤6 y	0.0057 (0.0005—0.0108)	0.0304	0.0016 (0.0050—0.0083)	0.6289	0.0013 (0.0053—0.0079)	0.7076
>6 y	0.0138 (0.0091—0.0185)	<0.0001	0.0122 (0.0062—0.0183)	<0.0001	0.0125 (0.0065—0.0186)	<0.0001
BMI						
<24	0.0190 (0.0130～0.0249)	<0.0001	0.0160 (0.0082～0.0237)	<0.0001	0.0160 (0.0082～0.0237)	<0.0001
24—27	0.0071 (0.0014～0.0128)	0.0143	0.0053 (0.0020～0.0127)	0.1561	0.0054 (0.0020～0.0127)	0.1515
>27	0.0042 (−0.0017～0.0102)	0.1650	0.0017 (−0.0060～0.0094)	0.6696	0.0012 (−0.0064～0.0088)	0.7496
eGFR						
≤60	0.0095 (0.0052～0.0138)	<0.0001	0.0078 (0.0014～0.0141)	0.0169	0.0082 (0.0018～0.0145)	0.0117
>60	0.00121 (0.0057～0.0185)	0.0002	0.0089 (0.0025～0.0154)	0.0064	0.0088 (0.0024～0.0152)	0.0069
Use of glucose-lowering drugs						
Only diet control	0.0102 (−0.0043～0.0247)	0.1683	0.0100 (−0.0102～0.0301)	0.3321	0.0093 (−0.0111～0.0297)	0.3717
Only OAD	0.0095 (0.0057～0.0133)	<0.0001	0.0066 (0.0017～0.0115)	0.0090	0.0064 (0.0015～0.0113)	0.0108
Only insulin	0.0197 (0.0041～0.0353)	0.0134	0.0248 (0.0062～0.0434)	0.0092	0.0255 (0.0070～0.0441)	0.0071
OAD + insulin	0.0087 (−0.0039～0.0213)	0.1754	0.0002 (−0.0166～0.0163)	0.9816	0.0003 (−0.0162～0.0167)	0.9760

Model 2: adjust for age, sex, diabetes duration, BMI, eGFR, and smoking.
Model 3: adjust for model 2, use of lipid-lowering, antihypertension, and glucose-lowering drugs.

outdoor activity during periods with colder temperatures in their diabetic patients. This is understandable because physical activity has been found to be lower during winter and increased during warmer months.[25] We also found an increase in body weight during the colder periods in our study population (data not shown), which is consistent with decreased physical activity and the increased calorie intake. Chen et al[11] reported that Chinese patients with type 2 diabetes have poorer glycemic control during holidays. There are a series of holidays that may present patients with more opportunity for greater calorie consumption, such as the mid-autumn festival with its big dinners and traditional high-caloric "moon cakes" and candies, Christmas with its traditional big dinners, candies and cookies, New Year with its party snacks and alcoholic beverages, and Chinese New Year with the traditionally elaborate dinners with family members over several days and consumption of candies and snacks on visits to the homes of friends and relatives, and the Lantern Festival with the traditional consumption of sweet glutinous rice dumplings. Not only diabetic patients, but also most others relax vigilance and pay less attention to glycemic control during these periods. Some physiologic and endocrine factors have seasonal variation also. For example, plasma glucagon and free fatty acid levels are higher in winter and have been associated with ambient temperatures.[26] Plasma cortisol concentrations and glucocorticoid activity are higher in winter.[27] Some studies also reported that vitamin D and melatonin affect glucose tolerance and insulin sensitivity.[28,29]

Previous studies have rarely focused on which patients would characteristically be at higher risk for this effect. Although all subpopulations in this study experienced temperature-associated HbA1c variability, some of them were particularly more susceptible to the effect of temperature than others. Few studies have evaluated the gender differences in HbA1c during temperature changes. One study by Carney et al[13] reported that women had higher seasonal HbA1c variability than men. In our study, we found the glycemic control in male and female groups to be influenced by the temperature, with HbA1c change seemingly greater in number in men. The interaction of sex and seasonal effect was assessed, but we found no significant effect between sex and seasonal effect ($p = 0.1264$ in the continuous model). One reason for this difference may be related to gender-dependent lifestyle patterns and physiological response to temperature. One study investigating seasonal effect in men and women found that men consumed more kilocalories, carbohydrate, sugar, and starch than women in cold temperatures.[30] Another study by Kuroshima et al[26] demonstrated glucagon levels to be higher in men than women, and insulin sensitivity was reduced in the winter season.

Patients younger than 65 years tended to have greater HbA1c changes during temperature decreases in this study. The exact reason for the phenomenon is not known. Adherence to medical recommendations should be considered. One study by Curkendall et al[31] showed that type 2 diabetes patients who were older (aged $>$ 65 years) were more likely to be compliant. In our study, patients who had DM for $>$6 years were more prone to HbA1c variability than those who had it for shorter durations, a finding that might be explained by an increase in beta cell dysfunction that occurs with disease progression. In addition, in our study, patients with lower BMI were more prone to the HbA1c variability than the patients with higher BMI. The precise mechanisms underlying these fluctuations are not known. One investigation performed in a Chinese population reported an association between higher BMI and higher insulin secretion as well as beta cell function.[32] Higher insulin secretion may compensate for the increases in dietary intake during seasonal reductions in temperature. Another reason might be related to medical attention. Overweight or obese diabetic patients were being treated at our medical facility, which provides a comprehensive diabetes care program that includes dietary consultation. Overweight or obese patients in this program are educated on ways to reduce weight and control calories in daily practice. These patients may have been paying more attention to dietary and lifestyle patterns. The clinicians as well as the thinner patients may have overlooked diet and weight education part of the program, thinking it was unnecessary. This is conjecture, of course, and would require further research to study the possible connection between diet and seasonal variability in HbA1c.

This study has some limitations. First, we recorded the corresponding class of glucose-lowering drugs (e.g., sulfonylurea, metformin, thiazolidinedione) at the same time we recorded the biochemical data. Hence, we could adjust the class of the glucose-lowering drugs in the analysis and reduce the confounding from antidiabetic medications. Although we recorded which drug classes were being taken at each time, we did not record the dosage of those drugs, which may have confounded our results. Generally, the physicians in Taiwan follow the recommendations by The Diabetes Association of the Republic of China and adjust the antidiabetic medications to achieve the glycemic goals. Even under these circumstances, the temperature effect on HbA1c still existed in the present study. We believe the temperature should play some role in the glycemic control in type 2 diabetes in Taiwan. Furthermore, we tried to minimize the bias by enrolling patients who had been regularly followed up at our clinics at least for 6 months, as they were probably taking relatively more stable doses of glucose-lowering agents. Second, we performed sensitivity analysis for seasonal effects. The receiver operating characteristic curve showed that the area under the curve (AUC) was 0.518 ($p < 0.001$, figure not shown). Although the p-value suggests significance, the AUC belongs to low discrimination area. The impact of temperature on the glycemic control in Taiwan seems to be limited. Taiwan is located in a subtropical area and the range of the temperature is relatively narrow, which may limit the tests' discriminate ability. Third, it is difficult for the present study design to identify key determinants of the temperature effect, one being temperature itself or other factors associated with the temperature. Future study may be needed to record the physical exercise level, diet calorie, hormone level, and other possible factors in detail to clarify the effect.

In conclusion, this observational follow-up study found a negative correlation between HbA1c and temperature in

4399 Taiwanese patients with type 2 diabetes, especially patients below 65 years old, those with diabetes for over 6 years, and those with lower BMIs. These findings suggest that clinicians might want to take HbA1c variability into account when treating diabetes, especially for those more at risk.

Acknowledgments

We thank James F. Steed (Di Jian-shi) for editing the English language and reviewing the manuscript.

References

1. Standards of medical care in diabetes—2011. *Diabetes Care* 2011;**34**(Suppl. 1):S11—61.
2. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;**321**:405—12.
3. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;**358**:2560—72.
4. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;**360**(2): 129—39.
5. Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**:2545—59.
6. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EAM, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA Diabetes Trials: a position statement of the American Diabetes Association and a Scientific Statement of the American College of Cardiology Foundation and the American Heart Association. *Diabetes Care* 2009;**32**:187—92.
7. Hinde FR, Standen PJ, Mann NP, Johnston DI. Seasonal variation of haemoglobin A1 in children with insulin-dependent diabetes mellitus. *Eur J Pediatr* 1989;**148**:597—9.
8. Ishii H, Suzuki H, Baba T, Nakamura K, Watanabe T. Seasonal variation of glycemic control in type 2 diabetic patients. *Diabetes Care* 2001;**24**:1503.
9. Gikas A, Sotiropoulos A, Pastromas V, Papazafiropoulou A, Apostolou O, Pappas S. Seasonal variation in fasting glucose and HbA1c in patients with type 2 diabetes. *Prim Care Diabetes* 2009;**3**:111—4.
10. Garde AH, Hansen AM, Skovgaard LT, Christensen JM. Seasonal and biological variation of blood concentrations of total cholesterol, dehydroepiandrosterone sulfate, hemoglobin A(1c), IgA, prolactin, and free testosterone in healthy women. *Clin Chem* 2000;**46**:551—9.
11. Chen HS, Jap TS, Chen RL, Lin HD. A prospective study of glycemic control during holiday time in type 2 diabetic patients. *Diabetes Care* 2004;**27**:326—30.
12. Dasgupta K, Chan C, Da Costa D, Pilote L, De Civita M, Ross N, et al. Walking behaviour and glycemic control in type 2 diabetes: seasonal and gender differences—study design and methods. *Cardiovasc Diabetol* 2007;**6**:1—11.
13. Carney TA, Guy SP, Helliwell CD. Seasonal variation in HbA1c in patients with Type 2 diabetes mellitus. *Diabet Med* 2000;**17**: 554—5.
14. Mianowska B, Fendler W, Szadkowska A, Baranowska A, Grzelak-Agaciak E, Sadon J, et al. HbA(1c) levels in schoolchildren with type 1 diabetes are seasonally variable and dependent on weather conditions. *Diabetologia* 2011;**54**:749—56.
15. Tseng CL, Brimacombe M, Xie M, Rajan M, Wang H, Kolassa J, et al. Seasonal patterns in monthly hemoglobin A1c values. *Am J Epidemiol* 2005;**161**:565—74.
16. Higgins T, Saw S, Sikaris K, Wiley CL, Cembrowski GC, Lyon AW, et al. Seasonal variation in hemoglobin A1c: is it the same in both hemispheres? *J Diabetes Sci Technol* 2009;**3**:668—71.
17. Tien KJ, Hung HC, Hsiao JY, Hsu SC, Hsin SC, Shin SJ, et al. Effectiveness of comprehensive diabetes care program in Taiwanese with type 2 diabetes. *Diabetes Res Clin Pract* 2008; **79**:276—83.
18. Lu C-H, Wu T-J, Shih K-C, Ni E, Reed V, Yu M, et al. Safety and efficacy of twice-daily exenatide in Taiwanese patients with inadequately controlled type 2 diabetes mellitus. *J Formos Med Assoc* 2013;**112**:144—50.
19. Li H-Y, Jiang Y-D, Chang C-H, Chung C-H, Lin BJ, Chuang L-M. Mortality trends in patients with diabetes in Taiwan: a nationwide survey in 2000—2009. *J Formos Med Assoc* 2012; **111**:645—50.
20. Lai Y-C, Wang C-S, Wang Y-C, Hsu Y-L, Chuang L-M. Falsely decreased HbA1c in a type 2 diabetic patient treated with dapsone. *J Formos Med Assoc* 2012;**111**:109—12.
21. Chang C-H, Jiang Y-D, Chung C-H, Ho L-T, Chuang L-M. National trends in anti-diabetic treatment in Taiwan, 2000—2009. *J Formos Med Assoc* 2012;**111**:617—24.
22. Sohmiya M, Kanazawa I, Kato Y. Seasonal changes in body composition and blood HbA1c levels without weight change in male patients with type 2 diabetes treated with insulin. *Diabetes Care* 2004;**27**:1238—9.
23. Hawkins RC. Circannual variation in glycohemoglobin in Singapore. *Clin Chim Acta* 2010;**411**:18—21.
24. Sakura H, Tanaka Y, Iwamoto Y. Seasonal fluctuations of glycated hemoglobin levels in Japanese diabetic patients. *Diabetes Res Clin Pract* 2010;**88**:65—70.
25. Belanger M, Gray-Donald K, O'Loughlin J, Paradis G, Hanley J. Influence of weather conditions and season on physical activity in adolescents. *Ann Epidemiol* 2009;**19**:180—6.
26. Kuroshima A, Doi K, Ohno T. Seasonal variation of plasma glucagon concentrations in men. *Jpn J Physiol* 1979;**29**:661—8.
27. Walker BR, Best R, Noon JP, Watt GC, Webb DJ. Seasonal variation in glucocorticoid activity in healthy men. *J Clin Endocrinol Metab* 1997;**82**:4015—9.
28. Baynes KC, Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, glucose tolerance and insulinaemia in elderly men. *Diabetologia* 1997;**40**:344—7.
29. Cagnacci A, Arangino S, Renzi A, Paoletti AM, Melis GB, Cagnacci P, et al. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clin Endocrinol (Oxf)* 2001;**54**:339—46.
30. Behall KM, Scholfield DJ, Hallfrisch JG, Kelsay JL, Reiser S. Seasonal variation in plasma glucose and hormone levels in adult men and women. *Am J Clin Nutr* 1984;**40**(6 Suppl): 1352—6.
31. Curkendall SM, Thomas N, Bell KF, Juneau PL, Weiss AJ. Predictors of medication adherence in patients with type 2 diabetes mellitus. *Curr Med Res Opin* 2013;**29**(10):1275 —86.
32. Chen G, Liu C, Chen F, Yao J, Jiang Q, Chen N, et al. Body fat distribution and their associations with cardiovascular risk, insulin resistance and beta-cell function: are there differences between men and women? *Int J Clin Pract* 2011;**65**(5): 592—601.