SEASONAL VARIATION IN HEMOGLOBIN A1c IN KOREAN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Yoon Ji Kim,1* Seongkeun Park,2* Wangjin Yi,1 Kyung-Sang Yu,4 Tae Hyuk Kim,1 Tae Jung Oh,1 Jinwook Choi,2 and Young Min Cho1

1Department of Internal Medicine, Seoul National University College of Medicine, 2Institute of Medical and Biological Engineering, Medical Research Center, Seoul National University, 3Interdisciplinary Program for Bioengineering, Graduate School, Seoul National University, 4Department of Clinical Pharmacology and Therapeutics Seoul National University College of Medicine and Hospital, 5Department of Biomedical Engineering, Seoul National University, Seoul, Korea

*Yoon Ji Kim and Seongkeun Park contributed equally to this work.

Received: 6 November 2013
Accepted: 9 January 2014

Address for Correspondence:
Young Min Cho, MD
Department of Internal Medicine, Seoul National University College of Medicine, 101 Bahnak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82.2-2072-1965, Fax: +82.2-762-9662
E-mail: ymchomd@snu.ac.kr

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (No. 2010-0028631, No. 2011-0030815).

INTRODUCTION

Because the life of all animals, including humans, is constantly influenced by the environment, time-dependent variations in biological functions, such as circadian or circannual rhythm, are commonly found in animal physiology (1-3). Interestingly, seasonal variations are frequently observed in metabolism of mammals. The most striking example is the seasonal variation in glucose metabolism in the desert gerbil Psammomys obesus (sand rat), exhibiting nutritionally induced insulin resistance and hyperglycemia (4), which is observed in spring and autumn when the animal is in its natural habitat (5).

Glycemic variation has also been observed in humans. Hemoglobin A1c (HbA1c), which is the product of non-enzymatic glycation of the hemoglobin molecule and reflects the average plasma glucose concentrations over the previous 2-3 months (6), has been shown to exhibit seasonal variations in both type 1 and 2 diabetic patients. For example, seasonal variation in HbA1c was shown in young type 1 diabetic patients in Poland, with the highest values in winter and lowest values in summer (7); in children with type 1 diabetes in the U.K., with lower levels of HbA1c during the summer months (8); in type 2 diabetic veterans in the USA, with its peak during March to April and trough during September to October (9); and in Japanese diabetic patients with type 1 or type 2 diabetes, with the highest values in March and lowest values in August (10). These studies were performed mainly in the northern hemisphere. Intriguingly, a study encompassing multiple geographic regions, including Calgary, Edmonton, Wisconsin, Singapore, and Melbourne, revealed that HbA1c levels in subjects with or without diabetes were lowest during warmer seasons and highest during cooler seasons regardless of hemisphere (11), indicating that temperature or other seasonal factors may influence plasma glucose levels. Because Korea has four distinct seasons, we...
hypothesized that ambient temperature or season may affect the glycemic control of patients with type 2 diabetes. Therefore, in this study, we examined the association between HbA1c and calendar day and/or ambient temperature in Korean patients with type 2 diabetes who received various types of anti-diabetic treatments.

MATERIALS AND METHODS

Subjects and data collection
We retrieved data from electronic medical records of the Seoul National University Hospital from October 2007 to May 2011. Mean daily temperature data in the Seoul area during the study period were obtained from the Korea Meteorological Administration. The data collected from electronic medical records included age, sex, diagnosis, HbA1c, prescribed medications and residential addresses. In total, we collected 128,284 HbA1c values measured using high performance liquid chromatography (Variant II Turbo, Bio-Rad, San Francisco, CA, USA) from 14,689 patients (Fig. 1). We excluded subjects if: 1) age < 30 yr; 2) patients had type 1 diabetes; 3) patients were treated with immunosuppressants, diagnosed with cancer or had been hospitalized during the study period; and 4) HbA1c measurements were made fewer than three times per year. According to these criteria, 10,498 patients and 70,314 HbA1c observations were excluded. Therefore, a total of 4,191 patients (2,211 men and 1,980 women, 65 ± 10 yr old) and 57,970 HbA1c observations were subjected to the final analyses. The patients were classified into four categories arbitrarily determined according to baseline HbA1c: HbA1c < 7% (n = 1,727); 7% ≤ HbA1c < 9% (n = 2,148); 9% ≤ HbA1c < 11% (n = 274); and 11% ≤ HbA1c (n = 42). We also divided the patients into five groups based upon the type of anti-diabetic therapy as follows: a group using lifestyle modification alone (n = 166), a group using oral anti-diabetic drugs (OADs) (n = 3,022), a group using insulin therapy only (n = 172), a group using combined therapy of OADs and insulin (n = 186), and a group who changed treatment from OADs to add-on insulin therapy or insulin-only therapy (n = 645).

Statistical analysis
Statistical analyses were carried out using SAS software (SAS Institute, Cary, NC, USA). First, the time series analysis was used to find seasonality in HbA1c. Next, we performed a Spearman correlation analysis to evaluate the correlation between HbA1c and ambient temperature because neither variable followed a normal distribution. In the time series analysis, monthly mean HbA1c values were determined by averaging the middle 95% of HbA1c values over a one month interval after excluding the upper and lower 2.5% of the values. The time series analysis of monthly mean HbA1c values was modeled as a linear combination of time \( t \), \( \cos \ t \), \( \sin \ t \), \( \epsilon_1 \), and \( \epsilon_2 \). The coefficient of \( t \) represents a linear trend in HbA1c values corresponding to time change. The coefficients of \( \cos \ t \) and \( \sin \ t \) represent a cyclic pattern in HbA1c variation, such as seasonality. The noise terms \( \epsilon_1 \) and \( \epsilon_2 \) were derived separately from the first and second autoregressive parts of the time series model and represent the randomness of the HbA1c values. The total time series model was fitted to monthly mean HbA1c and coefficients, and correspon-

Fig. 1. Flow chart of patient selection and grouping. n, number of patients; OADs, oral anti-diabetic drugs. *Add-on insulin therapy or insulin-only therapy.
The data are presented as the mean ± SD. 

The coefficients of cos t and sin t represent a cyclic pattern in HbA1c variability. 

The coefficient for cos t = -0.0743, P = 0.058). The differences between the highest and lowest HbA1c values (i.e., amplitudes) in a year were 0.16%-0.25%. However, a distinct seasonal variation in HbA1c was noticed in the subgroup using OADs only (the coefficient for cos t = -0.0949, P < 0.05), indicating that glycemic control was better in the warmer season and worse in the cooler season for this group of patients (Fig. 2B and Table 1).

**Correlation between HbA1c and temperature**

The Spearman correlation coefficient between daily mean HbA1c values and 3 month-moving averages of daily ambient temperature was measured (Table 2). Overall, the correlation coefficient between these two variables was -0.2154 (95% confidence interval [CI] -0.2711, -0.1580; P < 0.05), suggesting that a lower ambient temperature may have a negative influence on glycemic control in patients with type 2 diabetes. In subgroup analysis, however, this negative correlation was not statistically significant in subjects who were treated with lifestyle modification alone or insulin or whose baseline HbA1c was ≥ 11% (Table 2).
We observed a trend in seasonal variation in monthly averages of HbA1c with the highest values in February-March (late winter-early spring) and the lowest values in September-October (early autumn) in Korean patients with type 2 diabetes. Because the HbA1c value mirrors the average plasma glucose levels during the previous 2-3 months (6), these peak and trough HbA1c values reflect the mean plasma glucose levels during the winter and summer seasons, respectively. These results are consistent with previous reports showing maximum values of HbA1c in cooler seasons and minimum values in warmer seasons (7-12). In addition, the differences between the highest and lowest HbA1c values (i.e., amplitude) in a year were 0.16%-0.25%, which is also similar to the results of other studies, which reported amplitudes of 0.13%-0.45% (7, 9).

We examined the interaction between seasonal variation of HbA1c and types of anti-diabetic therapy or baseline HbA1c levels. Seasonal variations in HbA1c were observed only in patients who were treated with OADs, and this was not affected by baseline HbA1c values. It is of interest that HbA1c was not affected by ambient temperature in patients who were treated with either lifestyle modification alone or insulin. Perhaps this lack of effect means that glycemic control in relatively well-controlled type 2 diabetes is not affected by ambient temperature. In addition, patients using insulin therapy may effectively respond to the altered glycemic control by adjusting their insulin dosage. However, seasonal variations in HbA1c were also reported in healthy women (13) or patients who were treated with insulin (7, 9). Therefore, we cannot guarantee that patients who are treated with either lifestyle modification alone or insulin are less susceptible to seasonal changes in glycemic control. Furthermore, because the number of the patients in these subgroups was relatively small, we may have missed the actual signal of seasonal variation.

Although seasonal variations in HbA1c have been reported by several independent researchers (7-11), the mechanism underlying this phenomenon is still not definite. Our study was primarily concerned with the correlation between HbA1c and ambient temperature and the impact of sun exposure or different levels of physical activity in glucose homeostasis has not been considered. Nonetheless, serum 25-hydroxyvitamin D concentration, which is affected by exposure to ultraviolet light (14), or serum melatonin concentration, which is dependent on photoperiod (15), could play an important role. It was reported that vitamin D deficiency may increase insulin resistance and the risk of metabolic syndrome (16-18). Therefore, a lower serum level of 25-hydroxyvitamin D during the winter season (19) may aggravate glycemic control. Melatonin production is highest at night (20), and some studies reported seasonal variations in human melatonin production with increased levels in winter (15, 21). It was reported that the nighttime increase in melatonin was associated with rises in circulating glucose levels and reduced insulin sensitivity (22). However, there are studies showing that a lower level of melatonin was associated with development of type 2 diabetes (21, 23). Therefore, further studies are needed to examine the role of melatonin in the seasonal variations in HbA1c particularly in patients with type 2 diabetes.

Aside from seasonal biological variations, cultural events or food availability may influence the seasonal variability in HbA1c. In a Chinese study examining HbA1c during the Chinese New Year’s holiday, mean HbA1c was increased by 0.094% ± 0.828%, most likely due to decreased physical activity, increased intake of foods and/or increased consumption of alcoholic beverages (24). In addition, there is a tendency for increased intake of animal fat-containing foods and decreased physical activity in winter (25-27). Furthermore, it was reported that body mass index and waist circumference were higher in winter than in summer (28), which could be explained by changes in calorie intake and physical activity. These non-biological factors should be considered when evaluating seasonal variations in HbA1c because these factors could be modified by education and counseling.

Of interest, there was a decreasing secular trend of monthly averaged HbA1c values over time during the study period, as depicted in Fig. 2. This trend reflects the movement towards stricter glycemic control for patients with type 2 diabetes, which was supported by compelling evidence for the “legacy effect” of intensive glycemic control from the initial diagnosis of type 2 diabetes based on long-term follow-up in the U.K. Prospective Diabetes Study (29). Additionally, the Korean Diabetes Association recommended a target HbA1c level of < 6.5% in November 2007 (30), and this more stringent target level may have resulted in an improvement in HbA1c values during the study period.

### Table 2. Spearman correlation coefficient between 3-month moving averages of daily mean HbA1c values and daily ambient temperature

| Subgroups                                      | Spearman correlation coefficient (95% CI) |
|------------------------------------------------|------------------------------------------|
| Overall                                        | -0.2154 (-0.2711, -0.1580)*             |
| Subgroups according to the type of anti-diabetic treatment |                                     |
| Lifestyle modification alone                   | -0.0306 (-0.0965, 0.0356)               |
| OADs only                                      | -0.2122 (-0.2680, -0.1548)*             |
| Insulin therapy only                           | -0.0177 (-0.0825, 0.0473)               |
| Combined OADs and insulin                     | -0.0702 (-0.1333, -0.0064)*             |
| Changed from OADs to insulin therapy†         | -0.1320 (-0.1897, -0.0732)*             |
| Subgroups according to the baseline HbA1c     |                                         |
| HbA1c < 7%                                     | -0.1863 (-0.2428, -0.1284)*             |
| 7% ≤ HbA1c < 9%                                | -0.1469 (-0.2043, -0.0883)*             |
| 9% ≤ HbA1c < 11%                               | -0.0663 (-0.1272, -0.0048)*             |
| 11% ≤ HbA1c                                   | -0.0416 (-0.1474, 0.0653)               |

*P < 0.05; †Add-on insulin therapy or insulin-only therapy. CI, confidence interval; OADs, oral anti-diabetic drugs.
There are some limitations and strengths in our study. As mentioned earlier, we did not measure the level of sun exposure or physical activity, which may affect glucose homeostasis in patients with type 2 diabetes. The lack of data on 25-hydroxyvitamin D and melatonin prohibited us from examining the association between these hormones and glycemic control. However, the strength of our study is that we included more than 4,000 type 2 diabetic patients with HbA1c values measured on a regular basis by a standardized method in a single institution over 4 yr, which allowed us to examine the seasonal variation according to the different types of anti-diabetic therapy.

In conclusion, we observed a trend in seasonal variation in HbA1c in Korean patients with type 2 diabetes, particularly in the OAD-treated patients. Although the mechanism underlying this phenomenon is yet to be elucidated, stricter adherence to lifestyle modification and frequent assessment of glucose control appear to be necessary during the winter season to prevent aggravation of hyperglycemia in patients with type 2 diabetes.

ACKNOWLEDGMENTS

The statistical analyses in this paper were carried out with the help of the Medical Research Collaborating Center (MRCC) of Seoul National University Hospital.

DISCLOSURE

There is no conflict of interest to declare.

ORCID

Yoon Ji Kim http://orcid.org/0000-0001-9730-4120
Seongkeun Park http://orcid.org/0000-0002-4868-9404
Wangjin Yi http://orcid.org/0000-0002-7741-5525
Kyoung-Sang Yu http://orcid.org/0000-0003-0921-7225
Tae Hyuk Kim http://orcid.org/0000-0002-7975-2437
Tae Jung Oh http://orcid.org/0000-0002-5078-6123
Jinwook Choi http://orcid.org/0000-0002-9424-9944
Young Min Cho http://orcid.org/0000-0002-2331-6126

REFERENCES

1. Panda S, Hogenesch JB, Kay SA. Circadian rhythms from flies to human. Nature 2002; 417: 329-35.
2. Reppert SM, Weaver DR. Coordination of circadian timing in mammals. Nature 2001; 413: 199-205.
3. Bechtold DA, Loudon AS. Hypothalamic clocks and rhythms in feeding behaviour. Trends Neurosci 2013; 36: 74-82.
4. Ziv E, Kalman R, Herschkop K, Barash V, Shafrir E, Bar-On H. Insulin resistance in the NIDDM model Psmammomys obesus in the normoglycemic, normoinsulinemic state. Diabetologia 1996; 39: 1269-75.
5. Laraki M, Reusens B, Issoual D, Remacle C. Seasonal variations in the function of the endocrine pancreas in Psammomys obesus. Gen Comp Endocrinol 1998; 112: 255-61.
6. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lerman A, Metzger BE, Nathan DM. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care 2011; 34: e61-99.
7. Mianowska B, Fendler W, Szadkowska A, Baranowska A, Grzelak-Agciak E, Sadowski J, Koenen H, Mlynarski W. Hba1c(1) levels in schoolchildren with type 1 diabetes are seasonally variable and dependent on weather conditions. Diabetologia 2011; 54: 749-56.
8. Hinde FR, Standen PJ, Mann RP, Johnston DI. Seasonal variation of haemoglobin A1 and insulin-dependent diabetes mellitus. Eur J Pediatr 1989; 148: 597-9.
9. Tseng CL, Brimacombe M, Xie M, Rajan M, Wang H, Kolassa J, Crystal S, Chen TC, Pogach L, Safford M. Seasonal patterns in monthly hemoglobulin A1c values. Am J Epidemiol 2005; 161: 565-74.
10. Sakurai H, Tanaka Y, Iwamoto Y. Seasonal fluctuations of glycated hemoglobin levels in Japanese diabetic patients. Diabetes Res Clin Pract 2010; 88: 65-70.
11. Higgins T, Saw S, Sikaris K, Wiley CL, Cembrowski GC, Lyon AW, Kajuria A, Tran D. Seasonal variation in hemoglobin A1c is it the same in both hemispheres? J Diabetes Sci Technol 2009; 3: 668-71.
12. Maguire GA, Edwards OM. Seasonal variation in glycated haemoglobin in diabetics. Ann Clin Biochem 2001; 38: 59-60.
13. Garde AH, Hansen AM, Skovgaard LT, Christensen JM. Seasonal and biological variation of blood concentrations of total cholesterol, dehydroepiandrosterone sul fate, hemoglobin A1c, IgA, prolactin, and free testosterone in healthy women. Clin Chem 2000; 46: 551-9.
14. Norman AW. Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system. Am J Clin Nutr 1998; 67: 1108-10.
15. Reiter RJ. The melatonin rhythm: both a clock and a calendar. Experience 1993; 49: 654-64.
16. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. Am J Clin Nutr 2004; 79: 820-5.
17. Scragg R, Sowers M, Bell C; Third National Health and Nutrition Examination Survey. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 2004; 27: 2813-8.
18. Liu E, Meigs JB, Pittas AG, McKeown NM, Economos CD, Booth SL, Jacques PF. Plasma 25-hydroxyvitamin D is associated with markers of the insulin resistant phenotype in nondiabetic adults. J Nutr 2009; 139: 329-34.
19. Rapuri PB, Kinyamu HK, Gallagher JC, Haynatzka V. Seasonal changes in calcitropic hormones, bone markers, and bone mineral density in elderly women. J Clin Endocrinol Metab 2002; 87: 2024-32.
20. Pévet P. Melatonin: from seasonal to circadian signal. J Neuroendocrinol 2003; 15: 422-6.
21. Peschke E, Bühr I, Mühlbauer E. Melatonin and pancreatic islets: interrelationships between melatonin, insulin and glucagon. Int J Mol Sci 2013; 14: 6981-7015.
22. Cagnacci A, Arangino S, Renzi A, Paolotti AM, Melis GB, Cagnacci P, Volpe A. Influence of melatonin administration on glucose tolerance and...
insulin sensitivity of postmenopausal women. Clin Endocrinol (Oxf) 2001; 54: 339-46.

23. McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin secretion and the incidence of type 2 diabetes. JAMA 2013; 309: 1388-96.

24. 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.

25. Pivarnik JM, Reeves MJ, Rafferty AP. Seasonal variation in adult leisure-time physical activity. Med Sci Sports Exerc 2003; 35: 1004-8.

26. Dasgupta K, Chan C, Da Costa D, Pilote L, De Civita M, Ross N, Strachan I, Sigal R, Joseph L. Walking behaviour and glycemic control in type 2 diabetes: seasonal and gender differences-study design and methods. Cardiovasc Diabetol 2007; 6: 1.

27. Shahar DR, Yerushalmi N, Lubin F, Froom P, Shahar A, Kristal-Boneh E. Seasonal variations in dietary intake affect the consistency of dietary assessment. Eur J Epidemiol 2001; 17: 129-33.

28. Visscher TL, Seidell JC. Time trends (1993-1997) and seasonal variation in body mass index and waist circumference in the Netherlands. Int J Obes Relat Metab Disord 2004; 28: 1309-16.

29. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577-89.

30. Committee of clinical practice guideline: treatment guideline for diabetes. 1st ed. Seoul: MMK Communications; Korean Diabetes Association, 2007.