Int J Clin Exp Pathol 2016;9(9):9429-9435
www.ijcep.com /ISSN:1936-2625/IJCEP0035321

Original Article

Seasonal variations of hemoglobin A1c in residents of Beijing, China

Lina Zhang[1], Weiyi Li[2], Tongzhang Xian[1], Qi Pan[1], Ming Li[1], Lixin Guo[1]

[1]*Department of Endocrinology, Beijing Hospital, National Center of Gerontology, China;* [2]*Department of Endocrinology, Beijing First Hospital of Integrated Chinese and Western Medicine, Beijing, China*

Received July 8, 2016; Accepted July 20, 2016; Epub September 1, 2016; Published September 15, 2016

Abstract: Objective: Hemoglobin A1c (HbA1c) is routinely used to evaluate glycemic control in patients with diabetes. Using HbA1c of ≥ 6.5% for screening and diagnosis of type 2 diabetes is also recommended. The purpose of this study was to investigate seasonal variations of HbA1c in residents of Beijing city (China), including both diabetic and non-diabetic subjects. Methods: The study cohort included 61,167 HbA1c observations (HbA1c < 6.5%: n=36,174; HbA1c ≥ 6.5%: n=24,993) from residents who performed physical examination in Beijing Hospital over 5 years (from Jan 2007 to Apr 2011). We calculated monthly average HbA1c for both overall population and subpopulations defined by HbA1c values (HbA1c < 6.5% or HbA1c ≥ 6.5%). In addition, we analyzed whether there are any differences in HbA1c among subgroups divided by gender, age and time of blood specimen collection. Finally, general linear models (GLM) were applied to the data to assess the impact and potential interactions of various independent variables (age, time, month and gender) on the HbA1c changes. Results: For overall population, we observed a peak of HbA1c value (6.67%) in January and a trough (6.38%) in June to August. Surprisingly, it was noticed that the lowest value (6.36%) was in November. Similar monthly pattern was found in the subpopulations of HbA1c < 6.5%. For the subpopulations with higher values (HbA1c ≥ 6.5%), very slight changes were shown, with higher value (7.48%) in January to February and lower value (7.31%) in September. These seasonal fluctuations of monthly HbA1c values are statistically significant adjusted for all of the other factors in GLM analysis (age, time, and gender). Conclusion: In residents of Beijing, relatively higher HbA1c values in winter and lower values in summer were observed. In addition, the lowest HbA1c value was noticed in November, especially for subgroup of HbA1c < 6.5%. We think both geographical and cultural influences are directly related to HbA1c monthly variations. These findings have implications for epidemiologic studies and clinical assessment in both diabetic and non-diabetic populations.

Keywords: HbA1c, type 2 diabetes, seasonal variations

Introduction

As the prevalence of diabetes is increasing, the achievement of adequate glycemic control and prevention of chronic complications are getting more and more important [1, 2]. Hemoglobin A1c (HbA1c), also known as glycated hemoglobin, is a marker of glycemia and reflects the average blood glucose levels for the previous 60-90 days [3]. It has been estimated that 50% of the HbA1c level was determined by the plasma glucose level during the preceding 30 days [4]. Therefore, HbA1c level is routinely used to monitor the long-term glycemic control in individuals with diabetes and serves as an indicator for future risk of complications [5, 6]. It is also recommended by an International Expert Committee to use the A1c test to diagnose diabetes, with a threshold of ≥ 6.5% [7].

Increasing evidences suggest that glycemic levels, as shown by the HbA1c levels, exhibit a seasonal pattern in both type 1 and type 2 diabetic patients [8-17]. The phenomenon of lower levels of HbA1c during the summer months has been observed in children with type 1 diabetes in both Poland and U.K. [9, 15]. In addition, fluctuation of higher in winter and lower in summer of HbA1c value was reported in type 2 diabetic patients in Greece and Portugal, respectively [13, 17]. Overall, most of these studies were performed in the northern hemisphere with significant differences between winter and summer temperatures. A further study encompass-

Table 1. Monthly mean HbA1c values in Beijing residents from Jan 2007 to Apr 2011 (n=61,167)

Month	N (Total)	HbA1c (%) Mean ± SD	HbA1c < 6.5% N, (%)	HbA1c ≥ 6.5% N, (%)
January	3803	6.67 ± 1.13[a]	1932, (51)	1871, (49)
February	3895	6.60 ± 1.15[b]	2101, (54)	1794, (46)
March	6701	6.54 ± 1.10[b]	3816, (57)	2885, (43)
April	6513	6.44 ± 1.07[c]	4014, (62)	2499, (38)
May	5097	6.43 ± 1.07[c,d]	3124, (61)	1973, (39)
June	4908	6.38 ± 1.04[d]	3076, (63)	1832, (37)
July	4762	6.38 ± 1.03[c,d]	2976, (62)	1786, (38)
August	4879	6.38 ± 1.01[c]	3084, (63)	1795, (37)
September	4890	6.44 ± 1.00[b]	2865, (59)	2025, (41)
October	4826	6.43 ± 1.06[c,d]	2904, (60)	1922, (40)
November	5418	6.36 ± 1.08[e]	3378, (62)	2040, (38)
December	5475	6.60 ± 1.12[b]	2904, (53)	2571, (47)

Superscript letters (a, b, c, d, e) indicate statistically significant differences between the subgroups of month. Means sharing the same superscript are not significantly different from each other (P > 0.05). Different superscript indicates significant difference between the subgroups (P < 0.05).

ing 5 different geographic locations demonstrated that smaller differences between the lowest and highest HbA1c mean monthly value was shown in location with less variation in temperature over the course of the year like Singapore [18]. Several studies from Asia, like Korea [16], Japan [14] and Taiwan [12], have revealed seasonal pattern of HbA1c in diabetic patients. However, fluctuations in HbA1c levels by climatic change have not been reported for large populations of people in China, and whether these fluctuations differ by subject characteristics such as gender, age, or time of blood specimen collection is not known.

In our study, to evaluate whether there is a seasonal change of HbA1c levels in residents of Beijing City, China, we examined the association between mean values of HbA1c and time (calendar month) in subjects including both diabetic and non-diabetic populations for a five year-period.

Materials and methods

Subjects and data collection

We retrieved data from electronic medical records of the residents who performed physical examination in Beijing Hospital from Jan 1st, 2007 to Apr 30, 2011. Beijing is located in northeastern China and has a temperate and continental monsoon climate. The highest mean monthly temperature is in July at an average of 26°C (79°F), while the lowest was in January at an average of -4°C (25°F).

Both non-diabetic subjects and diabetic subjects with anti-diabetic therapy, using lifestyle modification, oral anti-diabetic drugs, insulin therapy and combined therapy, were included. The data collected from electronic medical records contain information of age, gender, diagnosis, HbA1c, prescribed medications. In total, we collected 190,945 HbA1c values measured using ultra2™ HbA1c analyzer (Primus Corp., Kansas, USA), which is based on boronate affinity chromatography method. Commercial lyophilized human whole blood (Lyphochek® Diabetes Control, Cat. No. 740, Bio-Rad Laboratories, USA) was used as a periodic quality control. To keep the results consistent, re-calibration was performed if quality control results exceeded the target value of 0.1%. For our analyses, we excluded subjects if: 1) patients with fever and infection; 2) patients with severe kidney disease, diabetic ketoacidosis and hyperosmolar hyperglycemic state; 3) patients with thyroid dysfunction, severe anemia, leukemia and other diseases that affect metabolism. According to these criteria, a total of 61,167 HbA1c observations (HbA1c < 6.5%: n=36,174; HbA1c ≥ 6.5%: n=24,993) were subjected to the final analyses. We also divided the patients into subgroups by gender, age and time of blood specimen collection.

Statistical analysis

To determine whether there were differences among multiple subgroups, one-way ANOVA or Kruskal-Wallis test with post hoc analysis using Student-Newman-Keuls (SNK) test were used. The HbA1c observations were stratified into two categories determined according to HbA1c: HbA1c < 6.5% and HbA1c ≥ 6.5%. General linear models (GLM)-multivariate analyses with type III sum of squares, was performed, which using HbA1c as dependent variable and gender, age, time and month as independent variables. Statistical analyses were carried out using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA) and differences were considered to be statistically significant at $P < 0.05$ level.

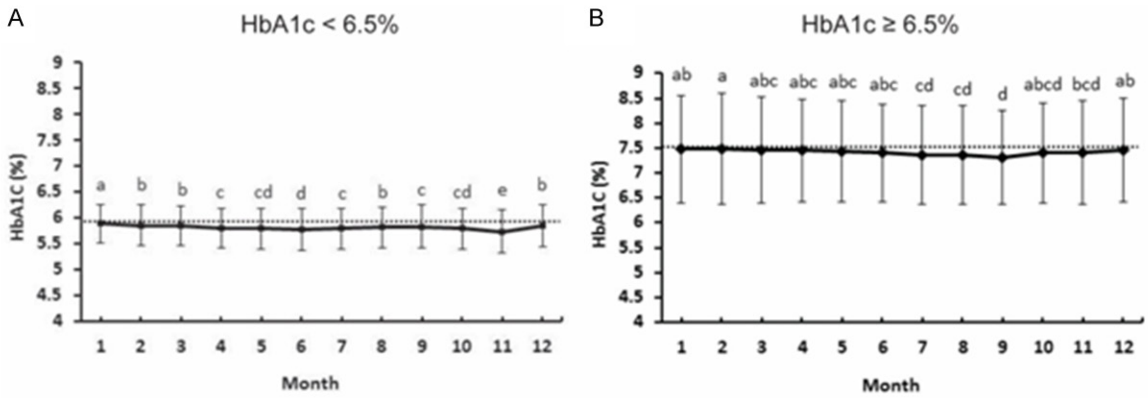

Figure 1. Time series of changes in HbA1c monthly average values in the subgroups stratified according to HbA1c: HbA1c < 6.5% (A) and HbA1c ≥ 6.5% (B). Same letters in the figure indicate no significant difference between the means of the groups analyzed (P > 0.05). Different letters indicate significant difference between the means of the groups analyzed (P < 0.05).

Table 2. Comparisons of HbA1c (%) between gender subgroups

Gender	All		HbA1c < 6.5		HbA1c ≥ 6.5	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Female	32,119	6.46 ± 1.06[a]	19,027	5.82 ± 0.40[a]	13,092	7.40 ± 1.02[a]
Male	29,048	6.47 ± 1.09[a]	17,147	5.79 ± 0.40[b]	11,901	7.44 ± 1.04[b]

Superscript letters (a, b) indicate statistically significant differences between gender subgroups. Means sharing the same superscript are not significantly different from each other (P > 0.05). Different superscript indicates significant difference between the subgroups (P < 0.05).

Table 3. Comparisons of HbA1c (%) between age subgroups

Age	N (Total)	HbA1c (%) Mean ± SD	HbA1c < 6.5% N, (%)	HbA1c ≥ 6.5% N, (%)
Age < 30	1751	5.56 ± 0.78[a]	1628, (93)	123, (7)
30 ≤ age < 40	5614	5.69 ± 0.85[b]	5090, (91)	524, (9)
40 ≤ age < 50	8049	6.15 ± 1.11[c]	6015, (75)	2034, (25)
50 ≤ age < 60	15200	6.57 ± 1.08[d]	8537, (56)	6663, (44)
60 ≤ age < 70	15355	6.64 ± 1.02[e]	8030, (52)	7325, (48)
70 ≤ age < 80	11463	6.73 ± 0.97[f]	5219, (46)	6244, (54)
80 ≤ age	3735	6.79 ± 1.00[g]	1655, (44)	2080, (56)

Superscript letters (a, b, c, d, e, f, g) indicate statistically significant differences between age subgroups. Means sharing the same superscript are not significantly different from each other (P > 0.05). Different superscript indicates significant difference between the subgroups (P < 0.05).

Results

Monthly variations in HbA1c values

Overall, in total of 61,167 HbA1c observations collected from Beijing residents during Jan 2007 to Apr 2011 (**Table 1**), we observed a peak of the highest monthly HbA1c level in January (6.67 ± 1.13%), slightly lower in December (6.60 ± 1.12%) and February (6.60 ± 1.15%). On the other hand, we found a trough of lower levels in June to August (6.38 ± 1.04%, 6.38 ± 1.03%, 6.38 ± 1.01%, respectively). The differences between the highest and lowest HbA1c values were about 0.29%. Surprisingly, the lowest level of the whole year was noticed in November (6.36 ± 1.08%). In further analyses, we divided the data into two subgroups according to HbA1c: HbA1c < 6.5% (n=36,174) and HbA1c ≥ 6.5% (n=24,993). Then, we found similar monthly pattern of HbA1c values in the subgroup of HbA1c < 6.5% (**Figure 1A**), which reflected the whole trend due to the higher proportion of this group in the whole observations in each month (**Table 1**). However, for the higher HbA1c group (HbA1c ≥ 6.5%), the changes between each month were not remarkable (about 0.17%), with higher value in January (7.48 ± 1.08%) to February (7.48 ± 1.12%) and lower value (7.31 ± 0.94%) in September (**Figure 1B**).

Comparisons among subgroups divided by gender, age and time of blood specimen collection

Overall, there was no difference in HbA1c levels between 32,119 female subjects (6.46 ± 1.06%) compared to 29,048 male subjects

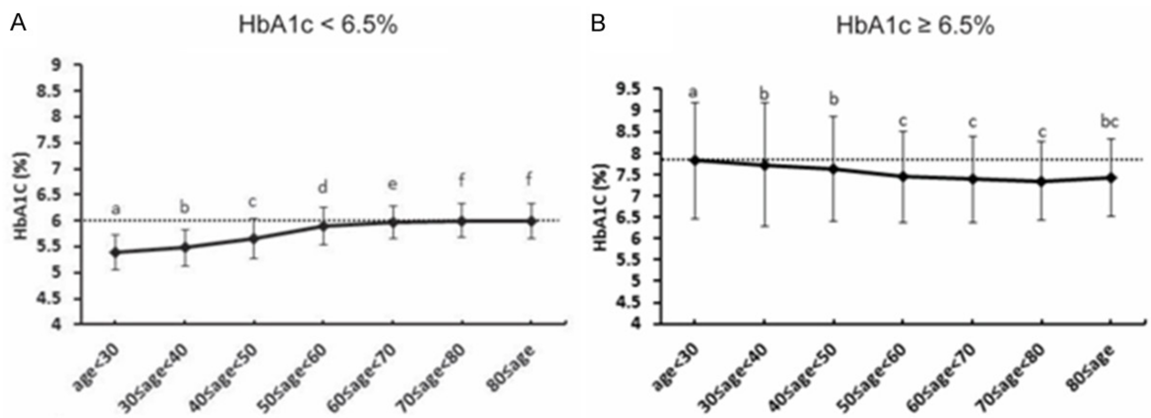

Figure 2. Variations of HbA1c value in different age groups in the subgroups stratified according to HbA1c: HbA1c < 6.5% (A) and HbA1c ≥ 6.5% (B). Same letters in the figure indicate no significant difference between the means of the groups analyzed (P > 0.05). Different letters indicate significant difference between the means of the groups analyzed (P < 0.05).

Table 4. Comparisons of HbA1c (%) between subgroups divided by time of blood specimen collection

Time	All		HbA1C < 6.5		HbA1C ≥ 6.5	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
8 AM	3384	6.63 ± 1.13[a,b]	1808	5.87 ± 0.39[a,b]	1576	7.51 ± 1.07[a]
9 AM	7533	6.55 ± 1.06[a,b]	4274	5.90 ± 0.38[a,b]	3259	7.42 ± 1.04[a]
10 AM	16145	6.15 ± 0.98[b]	11660	5.68 ± 0.40[b]	4485	7.37 ± 0.99[a]
11 AM	14896	6.43 ± 1.04[a,b]	8935	5.80 ± 0.40[a,b]	5961	7.38 ± 0.99[a]
12 PM	9970	6.70 ± 1.09[a,b]	4910	5.93 ± 0.36[a,b]	5060	7.44 ± 1.05[a]
1 PM	3577	6.74 ± 1.10[a,b]	1706	5.96 ± 0.33[a]	1871	7.45 ± 1.08[a]
2 PM	1948	6.84 ± 1.13[a]	826	5.98 ± 0.34[a]	1122	7.48 ± 1.09[a]
3 PM	813	6.84 ± 1.09[a]	347	5.98 ± 0.36[a]	466	7.48 ± 1.00[a]
4 PM	459	6.83 ± 1.11[a]	201	5.97 ± 0.34[a]	258	7.50 ± 1.04[a]

Superscript letters (a, b) indicate statistically significant differences between time subgroups. Means sharing the same superscript are not significantly different from each other (P > 0.05). Different superscript indicates significant difference between the subgroups (P < 0.05).

(6.47 ± 1.09%) (**Table 2**). However, after we divided them into subgroups according to HbA1c < 6.5% and HbA1c ≥ 6.5%, there was significant difference between female subjects and male subjects. In the subgroup of HbA1c < 6.5%, HbA1c level was shown less in male group (5.79 ± 0.40%) compared to female group (5.82 ± 0.40%). In contrast, for subgroup of HbA1c ≥ 6.5%, less HbA1c value was found in female group (7.40 ± 1.02%) instead of male group (7.44 ± 1.04%) (**Table 2**). Actually, the difference between mean values of different gender subgroups was within 0.04%, which is a slight difference.

All of the HbA1c observations were divided into seven subgroups according to the age of the subjects (**Table 3**). Overall, increased HbA1c values were shown with the increased age. Then, in each age group, we divided them into subgroups of HbA1c < 6.5% and HbA1c ≥ 6.5%. In the lower HbA1c subgroup, HbA1c levels were increased with age, in which the highest values were seen in those aged 70-80 and over (**Figure 2A**). This trend is similar with the overall trend due to the higher proportion of these subjects in the whole population (**Table 3**). However, in the higher HbA1c subgroup, HbA1c levels were reduced with age and kept the same in subgroups with age more than 50 (**Figure 2B**).

We also examined if there was any difference of HbA1c values among different time of blood specimen collection (from 8 AM to 4 PM) (**Table 4**). Overall, HbA1c observations which were collected around 10 AM were shown less (6.15 ± 0.98%) compared with which were collected at the other times, and 27.5% (16,145 in totally of 58,725) of the blood sample were collected at this time. The higher value of around 6.84 ± 1.13% was shown from samples collected in the afternoon between 2 PM to 4 PM. In the lower HbA1c subgroup of HbA1c < 6.5%, similar trend was shown as the whole trend, with less

Table 5. Impact of age, time, month, gender on the HbA1c values analyzed by general linear models (GLM)

Source	DF	Type III SS	Mean Square	F Value	P
Intercept	1	557148.05	557148.05	557732	< 0.001
Age	6	5534.47	922.41	923.38	< 0.001
Time	8	1435.87	179.48	179.67	< 0.001
Month	11	294.63	26.78	26.81	< 0.001
Gender	1	60.64	60.64	60.71	< 0.001

variations between highest (5.98 ± 0.36%) and lowest (5.68 ± 0.40%) values. However, in the higher HbA1c subgroup of HbA1c ≥ 6.5%, there was no difference among each of the time subgroups.

General linear models (GLM)-multivariate analyses were applied to the data to assess the impact and potential interactions of various independent variables (age, time, month and gender) on the change in the HbA1c values (**Table 5**). These seasonal and monthly fluctuations of HbA1c values are statistically significant (P < 0.001) adjusted for all of the other factors in GLM analysis (age, gender and time of blood collection). Additionally, there is a strong influence of subject characteristics such as age, gender and time of blood collection on the HbA1c value changes.

Discussion

From the analyses of monthly HbA1c values in Beijing residents over almost five years, we observed a peak in cooler winter months of January and a trough in summer of June to August. Surprisingly, we noticed that the lowest value was in November. Similar monthly pattern was found in the subpopulations of HbA1c < 6.5%. For the subpopulations with higher values (HbA1c ≥ 6.5%), there was only very slight changes, with higher values in January to February and lower values in September.

Seasonal variations of HbA1c have been reported in several other studies, in which climate and local temperature was thought to be directly associated with HbA1c changes [12, 14, 16]. Beijing city (latitude 39° 54' North) has a temperate and continental monsoon climate, with four distinct seasons. The coldest month is January and the hottest month is July. Overall, our data found higher HbA1c values in January and lower HbA1c values in summer from June to August, which seems reversely related to temperature. The study conducted in one hospital of Portugal, which has similar latitude (41° 08' North), showed peak of HbA1c levels in January-February and trough in late-summer of August-September. Similarly, mean local temperature of this place ranges between an average minimum and maximum of 5.2°C and 25.7°C in January and August, respectively [17]. In another study in Seoul (latitude 37° 34' North), the Spearman coefficient between daily mean HbA1c values and 3 month-moving averages of daily ambient temperature was correlated, which suggesting that a lower temperature may have a negative influence on glycemic control in type 2 diabetic patients [16]. In addition, from the study of several different geographic areas including Marshfield, Edmonton, Melbourne, and Singapore, difference between the low and highest HbA1c mean value is thought related to the variation in temperature over the course of the year. Singapore showed the least difference in HbA1c mean value, which is possibly due to the very little variation (2.0°C) in mean monthly high temperature [18]. Tseng et al. also commented that the difference in HbA1c values was temperature related, with greater HbA1c changes noted when there were larger temperature differences [11]. The seasonal pattern in HbA1c was also observed in our study, which we think this phenomenon is also related to climate and temperature.

In addition to local temperature, we think cultural factors such as physical activity and dietary patterns are also related to the seasonal pattern of HbA1c. It has been shown that physical activity advice is associated with lower HbA1c, but only when combined with dietary advice [19]. In Beijing city, most of people typically choose exercise like jogging or running outdoors other than treadmill running inside the gym. So the average outside exercise is much less in cold winter compared that in summer. On the other hand, food intake is greater in the winter months and people like sitting around a steaming beef or lamb hot pot on a cold evening. During Chinese Lunar New Year holiday in January or February, the main traditional celebrations of the festival are eating at home or restaurant with families and friends. Both this physical exercise and dietary culture are thought contributed to the higher HbA1c values of Beijing residents in winter. For the small drop of monthly HbA1c values in November we noticed, a possible explanation for this is many people choose travel to some attractions either in Beijing or other places even abroad during the National Day holiday from Oct 1 to Oct 7 (Golden week). Decreased appetite may coincide with intense travel, which may cause less food intake, resulting in lower HbA1c levels in November. Since the population who travel during this holiday are mostly healthy people, we only found this phenomenon in lower HbA1c group (HbA1c < 6.5%), not in the higher HbA1c group (HbA1c ≥ 6.5%). Further questionnaire for physical exercise, dietary habit and travel experience would be helpful for confirming this speculation.

The seasonal variations of HbA1c levels in group of HbA1c ≥ 6.5% has smaller amplitude compared to that in lower HbA1c group, with a difference of 0.17% and 0.29%, respectively. Studies by Tseng et al. on US diabetic veterans in East Orange, New Jersey showed HbA1c values were higher in winter and lower in summer with a difference of 0.22 [11], which is comparable with our results. In contrast, Maguire et al. and Hajime et al. reported much bigger seasonal changes in diabetic patients at about 0.47-0.69 and 0.5, respectively [20, 21]. In non-diabetic subjects, MacDonald et al. showed amplitude about 0.7 [22]. However, all of these studies were conducted in population of a much smaller scale, which is less representative for the whole population.

In our study, we observed seasonal variations in HbA1c levels in Beijing residents including both diabetic and non-diabetic subjects. These fluctuations are likely attributable to climate, with higher HbA1c levels in winter and lower levels in summer, with a contrast of about 0.29%. A small drop in HbA1c values was noticed in November especially in group of HbA1c < 6.5%. Smaller mean amplitude of variation was shown in the group of HbA1c ≥ 6.5%. We suggest a combination of potential environmental, biologic and cultural factors, especially physical exercise and food intake patterns, may all contribute to this seasonal pattern of HbA1c. These findings may have implications for the diagnosis of diabetes based on HbA1c values, the assessment of the effects of treatments or interventions, and the design of clinical trials using HbA1c levels as their primary outcome.

Disclosure of conflict of interest

None.

Address correspondence to: Weiyi Li, Beijing First Hospital of Integrated Chinese and Western Medicine, 13 Jintai Road, Chaoyang District, Beijing, China. Tel: +86-13611284546; E-mail: liweiyiliweiyi1@163.com

References

[1] Vasudevan AR, Burns A, Fonseca VA. The effectiveness of intensive glycemic control for the prevention of vascular complications in diabetes mellitus. Treat Endocrinol 2006; 5: 273-86.

[2] Stolar M. Glycemic control and complications in type 2 diabetes mellitus. Am J Med 2010; 123 Suppl: S3-11.

[3] Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia 2007; 50: 2239-44.

[4] Tahara Y, Shima K. Kinetics of HbA1c, glycated albumin, and fructosamine and analysis of their weight functions against preceding plasma glucose level. Diabetes Care 1995; 18: 440-7.

[5] The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44: 968-83.

[6] Zoungas S, Chalmers J, Ninomiya T, Li Q, Cooper ME, Colagiuri S, Fulcher G, de Galan BE, Harrap S, Hamet P, Heller S, MacMahon S, Marre M, Poulter N, Travert F, Patel A, Neal B, Woodward M; ADVANCE Collaborative Group. Association of HbA1c levels with vascular complications and death in patients with type 2 diabetes: evidence of glycaemic thresholds. Diabetologia 2012; 55: 636-43.

[7] International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009; 32: 1327-34.

[8] Ferrie CD, Sharpe TC, Price DA, Surtees RA. Seasonal variation of glycosylated haemoglobin. Arch Dis Child 1987; 62: 959-60.

[9] 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.

[10] Asplund J. Seasonal variation of HbA1c in adult diabetic patients. Diabetes Care 1997; 20: 234.

[11] Tseng CL, Brimacombe M, Xie M, Rajan M, Wang H, Kolassa J, Crystal S, Chen TC, Pogach L, Safford M. Seasonal patterns in monthly hemoglobin A1c values. Am J Epidemiol 2005; 161: 565-74.

[12] Liang WW. Seasonal changes in preprandial glucose, A1C, and blood pressure in diabetic patients. Diabetes Care 2007; 30: 2501-2.

[13] 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.

[14] Sakura H, Tanaka Y, Iwamoto Y. Seasonal fluctuations of glycated hemoglobin levels in Japanese diabetic patients. Diabetes Res Clin Pract 2010; 88: 65-70.

[15] Mianowska B, Fendler W, Szadkowska A, Baranowska A, Grzelak-Agaciak E, Sadon J, Keenan H, Mlynarski W. HbA(1c) levels in schoolchildren with type 1 diabetes are seasonally variable and dependent on weather conditions. Diabetologia 2011; 54: 749-56.

[16] Kim YJ, Park S, Yi W, Yu KS, Kim TH, Oh TJ, Choi J, Cho YM. Seasonal variation in hemoglobin a1c in korean patients with type 2 diabetes mellitus. J Korean Med Sci 2014; 29: 550-5.

[17] Pereira MT, Lira D, Bacelar C, Oliveira JC, de Carvalho AC. Seasonal variation of haemoglobin A1c in a Portuguese adult population. Arch Endocrinol Metab 2015; 59: 231-5.

[18] Higgins T, Saw S, Sikaris K, Wiley CL, Cembrowski GC, Lyon AW, Khajuria A, Tran D. Seasonal variation in hemoglobin A1c: is it the same in both hemispheres? J Diabetes Sci Technol 2009; 3: 668-71.

[19] Umpierre D, Ribeiro PA, Kramer CK, Leitao CB, Zucatti AT, Azevedo MJ, Gross JL, Ribeiro JP, Schaan BD. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011; 305: 1790-9.

[20] Maguire GA, Edwards OM. Seasonal variation in glycated haemoglobin in diabetics. Ann Clin Biochem 2001; 38: 59-60.

[21] 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.

[22] MacDonald MJ, Liston L, Carlson I. Seasonality in glycosylated hemoglobin in normal subjects. Does seasonal incidence in insulin-dependent diabetes suggest specific etiology? Diabetes 1987; 36: 265-8.