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Review article 1

Climate's impact on hemoglobin A1c levels in type 2 diabetes mellitus patients: A systematic review

Amal A. Mohamed[1], Asmaa M. Mohamed[2], Mohamed O. Mahmoud[3], Reem Elmahdy[4], Randa I. Elshiha[5], Gamil M. Abdalla[6], Nada S. Ali [6*], Ibrahim T. Ibrahim[3*], Ghada Hussein[7], Hala H. Eldeeb[8], Dalia S. Elsayed[9], Ahmed M. Khatan[10], Gehan Hamdy Labib[11], Wafaa S. Mohamed Hegab[12]

[1] Biochemistry and Molecular Biology Department, National Hepatology and Tropical Medicine Research Institute, GOTHI, Cairo, Egypt
[2] Biochemistry Division, Chemistry Department, Faculty of Science, Fayoum University, Fayoum, Egypt
[3] Biochemistry Department, Faculty of Pharmacy, BeniSuef University, BeniSuef, Egypt
[4] Internal Medicine Department, Faculty of Medicine, Suez Canal University, Suez, Egypt
[5] Clinical and Chemical Pathology Department, National Nutrition Institute, Cairo University, Cairo, Egypt
[6] Biochemistry Department, Faculty of Pharmacy, Egyptian Russian University, Badr City, Egypt
[7] Clinical and Chemical Pathology Department, National Diabetes Institute, The General Organization for Teaching Hospitals and Institute, Cairo, Egypt
[8] Clinical Pathology Department, El-Sahel Teaching Hospital, Cairo University, Giza, Egypt
[9]Anesthesia Department, Matreya Teaching Hospital, GOTHI, Cairo, Egypt
[10] General surgery Department, Damanhour Medical National Institute, Egypt
[11] Researcher of Chest Diseases, Department of Internal Medicine, Research Institute of Medicine and Clinical Studies, National Research Centre
[12] Internal Medicine Department, National Diabetes Institute, The General Organization for Teaching Hospitals and Institute Cairo, Egypt
Correspondence to Nada S. Ali,
Biochemistry Department, Faculty of Pharmacy, Egyptian Russian University, Badr City, Egypt
Tel: +20 1008106609;
e-mail: nada-salah@eru.edu.eg

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Abstract

Management of Type 2 diabetes mellitus (T2DM) is essential to reduce the associated adverse outcomes. Hemoglobin A1c (HbA1c) provides an estimate of glycemia over a period from one to three months. HbA1c is recommended as a standard of care for monitoring and testing diabetes, especially among T2DM. However, HbA1c can be affected by various factors such as weather. This review aims to identify the impact of climate on HbA1c levels in patients with T2DM by reviewing the related original articles. Scientific databases were examined to search for related studies and use various related terms. The searching process wasn't limited to a definite publication year. The original included studies focused on T2DM patients, reporting levels of HbA1c in different seasons, and written in the English language. Based on the inclusion criteria, six studies were included with a total number of 12899 T2DM patients. The age range of patients was 20-90 years. Climate has a significant impact on HbA1c levels, and such levels vary between different seasons. However, it is not possible to determine the season that recorded the optimum values or reduced values of HbA1c due to the great heterogeneity across the studies.

Keywords: hemoglobin A1c, type 2 diabetes mellitus, climate, hot, cold

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Introduction

Diabetes mellitus (DM) is one of the most important health and medical issues globally.It requires adequate management for patients to maintain good control of glucose and avoid further consequences [1]. The goal of type 2 diabetes mellitus (T2DM) management is to reduce macroangiopathy and microangiopathyand the incidence of cardiovascular complications [2].

Hemoglobin A1c (HbA1c) provides an estimate of glycemia over a period from one to three months proportionately weighted to more recent periods. HbA1c is produced by non-enzymatic glycation of hemoglobin [3]. HbA1c is a minor subtype of Hb A that changes by adding glucose to the *N*-terminal amino acid of its beta globin chain. Throughout the lifecycle of the red blood cells (RBC), glucose is constantly attached to hemoglobin due to erythrocytes' high glucose permeability. It depends on the blood glucose concentration and how long the erythrocyte is exposed to blood glucose [4]. It has been demonstrated that plasma glucose levels over the previous 30 days correspond to 50% of HbA1c levels [5]. HbA1c is recommended as a standard of care for monitoring and testing diabetes, especially among T2DM [6].

Monitoring HbA1c is necessary as the reduction by 1% in the level of HbA1c results in declines of 14%, 37%, and 21% in myocardialinfarction, microvascular complications and diabetes-related mortality, respectively [7]. Among T2DM patients the target value of HbA1c ranges between 7% and 8% rather than 6.5% and 7% [8]. However, HbA1c can be affected by various factors such as weather (seasons) [9-14]. It has been demonstrated that controlling diabetes in winter is worse due to more eating and less exercise [15, 16]. The changes in HbA1c through the different seasons have been investigated in previous studies; however, there was no systematic review reported on the subject. So, this systematic review wasperformed to identify the impact of climate on HbA1c levels in patients with T2DM.

Searching strategy

This review was written in agreement with the PRISMA statement [17]. Scientific databases, including PubMed, Science Direct, and Google Scholar were examined to search to related studies. The searchinvolved using a various terms related to our subject, including" impact, effect, influence, T2DM, variations, change, HbA1C, glycosylated haemoglobin, temperature, climate, weather, high, low, hot and cold. Such terms were used in varied combinations to obtain all possible related studies; the search process wasn't limited to a definite publication year. All the obtained articles from this research were revised to prevent missing relevant studies.

Eligibility criteria

The obtained findings were initially explored using an automation tool to identify and exclude duplicate articles (n = 303) and articles deemed irrelevant based on predefined criteria, such as studies conducted on animal models (n = 199). After this automated exclusion process, the remaining records were manually screened for eligibility. During manual screening, studies were excluded if they focused on T1DM (Type 1 Diabetes Mellitus) patients, diabetic patients without specifying the type of diabetes, and mixed populations of T1DM and T2DM patients. Further manual refinement involved excluding studies assessing the impact of factors unrelated to HbA1c, such as the effects of the COVID-19 lockdown. Additionally, the following criteria were applied during manual assessment: retained only original full-text articles written in English, excluded non-original articles, such as case reports or reviews, excluded articles not available in full-text format, and excluded articles written in languages other than English. Finally, studies reporting unclear or overlapping data were excluded manually. A total of 6 studies met the eligibility criteria and were included in the review. The scheme of automated and manual exclusions is illustrated in the PRISMA flow diagram (Figure 1).

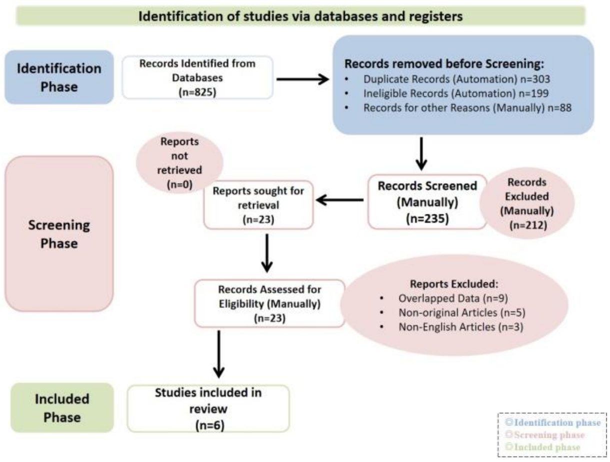

Fig. 1 Planning of eligible criteria

*The scientific databases, including PubMed, Science Direct, and Google Scholar.

Reviewing and analysis of data

The abstracts of the eligible studies were first reviewed to identify relevant data for extraction. Then, full-text articles were examined to extract the pre-determined data. The extracted data were initially recorded in an Excel sheet, reviewed for accuracy, and subsequently transferred to a pre-designed table for summarization.

This review included results from six studies based on the determined criteria [11, 18-22] (Table1).

Table 1 Summary of Studies on Seasonal Variations in HbA1c Levels

Author and Publication year	Study design/ Country	Sample size and characteristics	Results and main findings
Gholami et al., 2019 [18]	-Analytical cross-sectional -Iran	-N=402 -Gender: *Males=177 *Females=225 -Age:20-80 Y	*The mean level of HbA1c was significantly higher in autumn, and it was the lowest in winter (P=0.02). *The mean level of HbA1c in warm seasons was higher (7.72) compared to cold seasons (7.51) (P=0.047). *The proportion of patients with HbA1c ≥7% was significantly higher in warm seasons (P=0.015).
Kato et al., 2019 [19]	------- -Japan	-N=96 *Males=50 *Females=46	*HbA1c levels showed distinct seasonal patterns across the groups. Group A exhibited an increase from spring to summer, reaching the highest levels during the summer. In contrast, Group B demonstrated the highest HbA1c

		-Age: 21-90 Y *A:21-50Y *B:51-70Y *C:71-90Y	levels in spring, which then gradually declined through the year, reaching the lowest levels in winter. Meanwhile, Group C showed a steady decrease in HbA1c levels over the seasons, with the lowest levels observed in autumn.
Bando et al., 2019 [20]	------- -Japan	-N=89 -Gender: males -Age:21-90 Y	*There were seasonal changes in HbA1c levels. * Patients aged 21-50 Y showed the highest level in the summer; those with 51-70 Y had no elevation in summer, reduction in autumn and stability in winter; subjects with 71-90 exhibited gradual reduction from winter to autumn and elevation for winter. *For seasonal HbA1c changes, the impact of hot climate from spring to summer appeared for 21-50 years. *More activity in spring to summer related to 51-70 years. *Less exercise and more eating were observed for 71-90 years.
Hou et al., 2017 [21]	-Retrospective -China	-N=3722 -Gender: ---- -Age:20-79 Y *Youth=20-39Y *Middle=40-59Y *Elderly=60-79Y	*The HbA1c values were significantly higher in winter and significantly lower in summer. *Significant variance was found for HbA1c between men and women in the elderly category (P < 0.01). *HbA1c levels were comparable in youth and middle categories (P > 0.05) but considerably lower in the elderly one (P < 0.05). *Negative correlations of HbA1c with season (B=-0.05), age (B=-0.068), and gender (B=-0.04) were identified (P < 0.01).
Tien et al., 2016 [22]	-Observational follow-up -Taiwan	-N=4399 -Gender: *Males=2194 *Females=2205 -Age: mean=62.05 ±12.44	*A negative link was found between HbA1c and temperature (R =-0.475, P=0.001). *For every 1°C reduction in temperature, there was an increase in the risk of HbA1c level >7% (OR1.01, P < 0.001). *Individuals in the lowest quartile of temperatures (refers to those exposed to the coldest temperatures) had a greater risk of HbA1c > 7% compared to those in the highest quartile (refers to those exposed to the warmest temperatures) (OR: 1.13, P = 0.003) *Diabetics were at greater risk of HbA1C > 7% in the winter (aOR: 1.13, P=0.0027) and spring (aOR: 1.14, P= 0.0022) than those in the summer. *Following adjustment, patients younger than 65 years old (P=0.002), diabetes for longer than 6 years (p < 0.0001), and BMI < 24 were more susceptible to temperature changes (P< 0.0001).
Kim et al., 2014[23]	-Retrospective -Korea	-N=4191 -Gender: ------- -Age: ≥30 Y	*HbA1c showed its highest levels from February to March and its lowest levels from September to October (P=0.058). *A statistically significant seasonal difference was noted in the cases who received oral anti-diabetic drugs without insulin therapy (P< 0.05).

*Data is presented as numbers and percentages, OR: Odd ratio, aOR; adjusted odd ratio, BMI; Body mass index.

Two studies from Japan didn't report the study design [19, 20]The remaining four studies, which included analytical cross-sectional were from Iran [18], retrospective from China [21], observational follow-up from Taiwan [11], and retrospective from Korea [22]. The overall frequency of the patients was 12899 T2DM patients. There were two studies that didn't report the gender of the patients [21, 22], whereas the remaining four studies reported a total number of males of 2510 men, and one study enrolled 89 males only [20], whereas the total number of females is 2476 women. The mean age of patients was reported in one study [11], whereas the remaining five studies reported the age range of patients, which ranged between 20 years and 90 years. Two studies categorized patients based on age; both studies categorized patients into three age groups with variationsin age range of each group in each study [19, 21].

The results of the studies involved heterogeneous findings due to variations in study design, analysis and investigated correlations. However, we could identify the findings as follows:

Regarding the levels of HbA1c, the levels of HbA1c were found to be significantly higher in autumn [18], winter [21], from February to March [22], with increased risk of high HbA1c in winter (OR 1.13, P=0.0027)and spring (OR 1.14, P=0.0022), where the risk of increased HbA1c increased with the lowest temperature (OR 1.13, P=0.003) and the risk increased by one fold (OR1.01, P<0.001) when the temperature reduced by one degree [11]. The levels of HbA1c were found to be significantly lower in winter [18], summer [21], and from September to October [22].

Additionally, the mean levels of HbA1c were higher in warm seasons compared to cold ones (P=0.04), and the proportions of patients with high HbA1c were also higher in warm seasons (P=0.01) [18]. The impact of hot climate from spring to summer was detected among those aged 21-50 [20], and seasonal variation was noted among patients receiving oral anti-diabetic medications [22].

Other studies reported the change in HbA1c based on age groups and seasons. The youngest age group, exhibited high HbA1c from spring to summer [19] with a peak in summer [19, 20], whereas the older group exhibited the peak in spring with gradual reduction to winter [19], no increase in summer, reduction in autumn and stability in winter [20]. The oldest group exhibited gradual reduction in autumn [19], gradual reduction from winter to autumn and elevation in winter [20].

Regarding the factors affecting HbA1c, one study revealed that in elderly patients' significant variation was found between both genders (P<0.01), but HbA1c levels were comparable in youth and middle groups, and significantly lower among elderly one (P<0.05) [21]. There were significant negative correlations were found between HbA1c with the season (B=-0.05), age (B=-0.068), gender (B=0.04) [21], and temperature (R=-0.475) [11]. Susceptibility to temperature was associated with age younger than 65 years (P=0.002), diabetes duration for more than six years (P<0.0001), and BMI <24 (P<0.0001) [11].

HbA1c is a marker of cumulative glycemic exposure within a preceding period of 2-3 months [23]. Various physiologic parameters are known to be affected by seasonal cycles [24], such as heart rate, blood pressure, cortisol and insulin levels [25-27]. Additionally, climate change can affect blood glucose by inducing several events directly or indirectly leading to poor glycemic control [28]. This systematic review was established to identify the influence of climate on HbA1c levels in T2DM patients as there was no previous systematic review reporting this subject.

It was reported that worsened glycemic control among diabetic patients has been determined following exposure to colder temperature [29]. In the current analysis, the elevation of HbA1c was reported in winter in four studies [11, 21, 22] with an increased risk of high HbA1c of 1.13 fold. On the other hand, other studies revealed that in winter, there were significant reductions in HbA1c levels [18]. However, other studies reported heterogeneous findings based on age group, including reduction in winter [19], stability and elevation in winter [20]. Also, the control of diabetes was reported to be worse in the winter season due to reduced level of exercise and more eating habits [15, 16]. This was observed in one of our included studies among the oldest age group of 71-90 years due to less exercise and more eating [20].

Based on previous literature, there are variations in exercise practice and diet among diabetic patients which may lead to variability in controlling the glucose level [15]. In winter, the climate is cold and as a result, the patients are more predisposed to eat more and perform less exercise [16]. This explains why controlling diabetes may be worsening in winter [30]. There is no explanation regarding the reduction and stability of HbA1c. However, it could be proposed that age is a determinant that may affect HbA1c, and we found the impact of age in our analysis; in older groups of 51-70 years, more activity in spring to the end of summer may improve the levels of HbA1c that led to stability in winter [19]. However, in the oldest age group of 71-90 years, the patients experienced an elevation in winter due to less exercise and more eating with a gradual reduction from winter to autumn due to the reduction in spring and summer [20]. It was reported that the tendency to control blood sugar may vary in a wide range among diabetic patients due to variations in age, severity and the presence of social differences [20]. Additionally, we found a considerable negative correlation between HbA1c with age [21], and temperature [11].

One of the included studies demonstrated that there was a significant variation in HbA1c between both genders in elderly patients [21]. In a previous study, it was found that the levels of HbA1c among T2DM females were susceptible to temperature [31].

More studies reported that the levels of HbA1c in winter were higher than those in summer [32]. Another study revealed that among diabetic veterans, the values of HbA1c were higher in winter and lower in summer [14]. It is reasonable that HbA1c levels decrease in warmer seasons due to thsincreased activity and reduction of food intake. However, we found that higher HbA1c levels were reported in warmer seasons [18-20], spring [11, 19], and autumn [18]. On the other hand, a reduction of HbA1c in warmer seasons was reported in other studies [19, 20, 22]. It was reported that the regions with a large difference in temperature between winter and summer have more obvious seasonal variations of HbA1c [33]. Also, we found that susceptibility to temperature was associated with younger age, duration of diabetes and BMI [11]. This may indicate that there are several factors incorporated in HbA1c levels. Furthermore, it was suggested that there is a complex considerable biological, environmental and cultural factors involved in the impact of seasons on the levels of HbA1c [26]. Other literature suggested that air temperature, the impact of seasonal changes in hormones such as vitamin D are incorporated in seasonal variations of HbA1c [34, 35]. A previous study by Higgins et al. revealed that gender, smoking status and age affected the values of HbA1c [36]. However, the exact mechanism through which the different seasons induce changes in HbA1c levels is not fully understood [37].

The limitations of this review are the inclusion of few studies, and the heterogeneity of studies. The strengths include that it is the first systematic review report on the current subject declaring the gaps in research regarding the impact of climate on HbA1c levels and this will help to improve the quality and designof further studies. Therefore, further studies are recommended with the inclusion of larger sample size and the determination of predictors that may affect HbA1c. Also, further meta-analysis is highly recommended.

Conclusion

It could be concluded that the levels of HbA1c are varied between different seasons during the year. However, it is hard to determine in which season the optimum values of HbA1c could be recorded due to several factors, including the heterogeneity of the included studies such as variation in climates between different regions, the variation in reporting results and study population and characteristics, including age, diabetes duration, and assessment durations.

Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

A. A. M., M. O. M., A. M. K.and , R. E. researched data. R. I. E., G. M. A. and W. S. M. H., wrote the manuscript and researched the data. G. H., H. H. E., D. S., and I. T. I. contributed to reviewed/edited the manuscript. A.M.M., and N. S. A., wrote the first draft of the manuscript. All authors reviewed/edited the manuscript.

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