Seasonal variation of glycated hemoglobin A_{1c}% among diabetic patients in Mosul

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ABSTRACT

Objective: To determine the seasonal variation of glycemic level among diabetic patients in Mosul, and to define the seasons where blood glucose may surge or decline.
Patients and methods: An observational retrospective case series study of seven hundred HbA_{1c}% results pertaining to 653 randomly enrolled type 2 (96%), and type 1 (4%) diabetic patients which were collected over 28 consecutive months. The HbA_{1c}% mean of each month separately, and the HbA_{1c}% means of the months whose HbA_{1c} reflects the glycemic control of the preceding season were estimated, plotted, and statistically compared.
Results: The monthly HbA_{1c}% means throughout the study period comprised a sinusoidal curve with higher values between early spring (March) to early summer (June) and lower values between early autumn (September) to early winter (January) of each year. Throughout the study period, the mean HbA_{1c}% of all early springs (8.87% ± 1.57% SD) was the maximal, while the mean HbA_{1c}% of all early autumns (7.81% ± 0.94% SD) was the minimal.
Conclusion: Glycemic levels among diabetic patients in Mosul, as reflected by early spring's peak, and early autumn's trough of HbA_{1c}%, are highest during winter and lowest during summer.

الخلاصة

هـدف البحث: يهدف هذا البحث إلى بيان تأثير الفصول على مستوى كلوكوز الدم لدى السكريين في الموصل وتعيين الفصول التي قد يرتفع فيها مستوى كلوكوز الدم أو ينخفض.
طريقة البحث: اشتملت هذه الدراسة على ٧٠٠ فحص مختبري لنسبة خضاب الدم الكلوكوزي تعود لـ ٦٥٣ مريض سكري عشوائي الاختيار من النمط ٢ و١ خلال ٢٨ شهراً متتابعاً. ولقد تم حساب معدل نسبة خضاب الدم الكلوكوزي لكل شهر من أشهر فترة البحث على حده، وللأشهر التي يمثل معدل خضاب الدم الكلوكوزي فيها مستوى سكر الدم خلال الفصول السابقة لها. كما تمت جدولة النتائج ومقارنتها إحصائيا.
النتائـــج: شكلت المعدلات الشهرية لنسبة خضاب الدم الكلوكوزي منحنىً جيبياً يرتفع ما بين بداية الربيع (آذار) وبداية الصيف (تموز)، وينخفض ما بين بداية الخريف (آب) وبداية الشتاء (كانون ثاني) من كل عام. وكان معدل نسبة خضاب الدم الكلوكوزي لبدايات الربيع كلها (٨,٨٧% ± ١,٥٧) هو الأعلى خلال فترة البحث، فيما كان معدل نسبة خضاب الدم الكلوكوزي لبدايات الخريف كلها (٧,٨١% ± ٠,٩٤) هو الأوطأ.
الاستنتاج: إن مستوى سكر الدم لدى السكريين في الموصل، كما يعكسه ارتفاع نسبة معدلات خضاب الدم الكلوكوزي في بدايات الربيع وانخفاضه في بدايات الخريف، يبلغ مستواه الأعلى في فصل الشتاء والأوطأ في فصل الصيف.

Seasons affect body physiology in health and disease. Seasonal variation of sleeping metabolic rate, thyroid activity[1], serum cholesterol, free testosterone, prolactin[2], and hypertension[3,4] had all been reported. Studies on diabetes, generally

agreed on the finding that glycated hemoglobin A_{1c}% (HbA_{1c}%) vary seasonally; however, there were inconsistency in the results.

Garde et al (in 2000) found that HbA_{1c}% increases in autumn and in spring and decreases in winter and in summer[1], while Nordfelds and Ludrigsson (in 2000) showed that HbA_{1c}% of type 1 diabetes peaks in autumn and in winter and declines in spring and in summer.[5] Ishi et al (in 2001) found that the mean HbA_{1c}% is higher in winter compared with autumn.[6] Sohmiya et al (in 2004) reported higher levels of HbA_{1c}% in autumn and winter and lower level in spring and summer.[7] The last research in this regard was Tseng's et al (in 2004) at US that reported increasing values of HbA_{1c} in late winter to a peak in March-April, and decreasing values in late summer to a trough in September-October.[8] Seasonal variation in the last study was more marked at locations where winter-summer temperature difference is more than 50F°, and among those who had higher glycemic levels.[8]

Because of its clinical and therapeutic impact, seasonality of glycemic level among diabetic patients should be evaluated everywhere it is expected to be found in the world. Mosul, according to online Weather Reports Company, occurs at a latitude of 36°18´ N, a longitude 43° 12´ E, and an elevation of 732 ft. During winter (December-February) the average temperature is 6.6 C° (°F 44), with a light duration as short as (9.5) hours. During summer (June-August) the average temperature is 32.6° (°F 91), with a light duration as long as (14.5) hours.

The objective of this study is to determine the seasonal variation of glycemic level among diabetic patients of Mosul, and to define the seasons where blood glucose surges or declines.

Patients and methods

An observational retrospective case series study design was used to analyze data collected over 28 consecutive months between the 1st of December 2005 and the 31st of March 2008. It enrolled 700 HbA_{1c}% test results that pertain to 653 randomly enrolled diabetic patients. Ninety six per cent of the patients were type 2 (n 626), and 4% were type 1 (n 27). Males (n 268) constituted 41% and females (n 385) were (59%). The mean age (±SD) was 22 (±10.7) years for type 1, and 55.4 (±6.8) years for type 2. All of the enrolled patients were on oral hypoglycemic drugs and/or insulin. There were no exclusion criteria apart from evident hemoglobinopathies or uremia. All of HbA_{1c}% tests were primarily done for the sake of assessment and management of the patients, however, patients' consent was formally obtained.

Hemoglobin A_{1c}% of non fast intravenous blood samples, was colorimetrically quantitated, using standard solution as a reference (Stanbio laboratory, Texas USA). The tests were all conducted at one civil laboratory, and the data were all registered at one private clinic in Mosul. Most of HbA_{1c}% tests (n 621) were once achieved in the first visit of the patients, but 79 of them were repetitions of the test belonging to 32 patients. Because of the limited number of the study samples per month, sub grouping of the enrolled patients into sex, age, and disease duration was unfeasible.

Method of electing the months whose HbA_{1c}% best represents glucose levels of the preceding seasons:

Hemoglobin A_{1c}, a fraction of hemoglobin A, is glycated by non-enzymatic combination of ambient serum glucose to the terminal valine of beta chains.[9] Once glycated, HbA_{1c} will remain so all through the RBC life span (120 days), hence HbA_{1c}% testing at any time reflects the mean blood glucose of the preceding 8-12 weeks.

The RBC mass at any month can be arbitrarily divided into four generations. The oldest quarter is the one that has been synthesized about four months ago and going to vanish soon. The second is the one that has been synthesized about three months ago and will stay further one month. The third has been synthesized about two months ago and going to stay two months more, and the fourth is the one that has been thrown into the circulation about one month ago and going to survive for further 3 months.

Considering the above concept, it was concluded that March's mean HbA_{1c}% is the best representative of winter glycemia, as 75% of March's RBC mass has been synthesized, and glycated, during the preceding winter months (December, January, and February). Next to it in significance is the mean HbA_{1c}% of March and April together, as 68.75% of winter months' RBCs were synthesized in these two months, i.e. March and April.

June, accordingly, is the best representative of spring season, followed by June and July, September is the best representative of summer, followed by September and October, and December is the best representative of autumn, followed by December and January.

Because of the larger number of HbA_{1c}% tests in two months than in one month, that gives better statistical results, we elected the mean HbA_{1c}% of March-April, of June-July, of September-October, and of December-January, as representatives of winter, spring, summer, and autumn glycemic levels respectively. These months have been used for the same purpose in serious similar study.[8] The mean HbA_{1c}% of patients attending in each month, and the mean HbA_{1c} of patients attending in the representative months were estimated (±one SD). A t-test analysis was used to compare the numerical results and a P value <0.05 was regarded significant.

Results

The monthly means of HbA_{1c}%, throughout the study period, comprised a sinusoidal curve with higher values between March and July, and lower ones between September and January of each of the two study years (Fig. 1).

The mean HbA_{1c}% of all early spring months (i.e. March-April of 2006, and 2007) was the highest (8.87% ± 1.57), while the mean HbA_{1c}% of all early autumn months (i.e. September-October of 2006, and 2007) was the lowest (7.81% ± 0.94) during the study period, with a significant difference (P<0.001) (Table 1).

Considering each of the two study years separately, we found that the yearly rise and descent of HbA_{1c}% were nearly of similar chronological profile. The lowest level of 2006 (7.95% ± 0.9) and of the lowest level of 2007 (7.78% ± 0.98) were both in early autumn (September-October) of each year. However, the highest level of 2006 and the highest level of 2007 were, slightly, chronologically inconsistent. Whereas the peak of 2007 (9% ± 1.6) came in its expected time (in March-April), the peak of 2006 (9.25% ± 2.45) occurred slightly earlier (in December-January) (Table 2). In spite of the earlier peaking of 2006, March-April HbA_{1c}% mean of the same year (8.75% ± 0.15%) was significantly higher than September-October HbA_{1c}% mean (7.95% ± 0.9) (P<0.001) (Table 2).

Discussion

Our results, in regard to the pattern of seasonal variation, are consistent with what Tseng et al[8], Maguire-Edwards[10], and Ishi et al[6], found at US, UK, and Japan respectively. Considering the fact that HbA_{1c} at any time reflects the mean glucose level during the preceding 8-12 weeks, it is frank that glycemic level of diabetic patients in Mosul is highest in winter and lowest in summer (Table 1 and 2). The non congruent backward shift of 2006 HbA_{1c} peak to December 2005- January 2006 (Table 2) is possibly due to the smaller number of subjects (n 28) during December 2005 and January 2006, that produced an inconsistently high HbA_{1c}% figure. However, Nordfelds and Ludrigsson[5], likewise, reported a similar winter peaking of HbA_{1c}.

Some researchers has attributed seasonal fluctuation of blood glucose among diabetic patients to nutritional factors[11,12]. Others attributed it to seasonal variation of body weight[11,13,14], to physical activity [15,16], or to the direct effect of low ambient temperatures during winter.[8] The rise of blood glucose in winter is, however, not restricted to diabetic patients alone. Winter's rise of glycemic level was reported in normal people as well[17]. Being so, the matter seems to be an innate strategy of human physiology.

Winter rise of glucose level appears to be mediated by the counter regulatory hormones: cortisol, epinephrine, and thyroid hormones that had been extensively reported to increase during winter or cold stress. The morning

plasma cortisol, for example, had been found to be higher in winter than in summer.[18] Hansen and others, in this regard, also reported higher levels of cortisol during December-January in comparison to other months of the year.[18,19]. In respect to catecholamine role, adrenal medullectomized rats were shown to die faster than normal controls when exposed to cold stress.[20] Thyroid stimulating hormone (TSH), in its turn, is increased in laboratory animals by cold and decreased by heat.[20] Middle-aged and older men and women were proved to have significantly higher TSH levels in winter[21]. No studies were seen on glucagon or growth hormone seasonal variation.

Whatever the homeostatic purpose behind the winter rise of these hormones, and whatever the other functions they exert during winter, glucose level elevation during this season seems to be beneficial in serving heat production (thermogenesis) to combat winter cold, we speculate.

When the environmental temperature is lower than body temperature, the temperature control system institutes heat conserving procedures and increases thermogenesis.[22,23] Thermogenesis in human is achieved by muscle contraction, assimilation of food, and vital processes of basal metabolic rate (BMR).[21]

Shivering, an involuntary muscle contraction, is promoted during winter to provide heat, in addition to semiconscious increase of motor activity.[20] The energy in the muscles is liberated from hydrolysis of the compounds adenosine triphosphate (ATP), and, to a lesser extent, phosphoryl creatine (PC)[24]. After hydrolysis and energy liberation, ATP and PC are regenerated using energy provided by the breakdown of glucose to CO2 and H2O.[24] Glucose involvement in the regeneration of ATP and PC highlights the essential role of glucose in muscular thermogenesis during winter.

Basal metabolic rate, the other major thermogenic process, also increases in winter. Eskimo have been shown to have elevated BMR relative to predicted values. This elevation, has been postulated, to be a physiological adaptation to chronic and severe cold stress[25]. Sleeping metabolic rate was, as well, shown to be maximal in winter and minimal in summer[2]. Glucose role in promoting metabolic thermogenesis seems to be as essential as in the muscular thermogenesis. Hepatic glucose release was reported to positively correlate with BMR both in type 2 diabetes and in control subjects[26].

Inefficient thermogenesis in diabetes:

In diabetes, especially type 2, thermogenesis frankly looks inefficient for many reasons. First: insulin resistance reduces glucose uptake and energy expenditure irrespective of obesity[27]. Insulin resistance in diabetes is, as well, associated with a decreased sensitivity and responsiveness to norepinephrine in lab animals suggesting a reduced thermogenic capacity among diabetic patients[28]. Second: autonomic neuropathy that complicates uncontrolled diabetes, further contributes to thermogenic failure. Patients whose ß-adrenergic receptors are blocked by ß-adrenergic blockers had been found to have a lower BMR[29], suggesting the importance of autonomic nervous system in the metabolism**,** thence the thermogenesis. Young diabetic patients with autonomic neuropathy have, also, showed impaired thermoregulation to external cooling, even during metabolic stability, which may predispose to hypothermia[30]. Moreover, shivering, the involuntary autonomic activity that greatly contributes to thermogenesis during winter is expected to be hindered in diabetes. Tseng's finding of greater seasonal variation of blood glucose among the higher HbA_{1c} (>9%) subgroup[8] could be due to the higher prevalence of autonomic neuropathy among subjects of this subgroup. The depressed thermogenesis in diabetes, also, interprets the higher risk of hypothermia among elderly diabetic patients[31].

In conclusion, we believe that glucose rise in winter is a part of a normal thermoregulatory strategy in human, but, the depressed thermogenesis in diabetes leads to accumulation rather than making use of the winter rise of glucose, producing a marked winter glycemic surge.

Whatever the underlying mechanism, Mosul's diabetic patients and health providers should seriously consider glycemic rise in winter, and be aware of a reciprocal summer hypoglycemia.

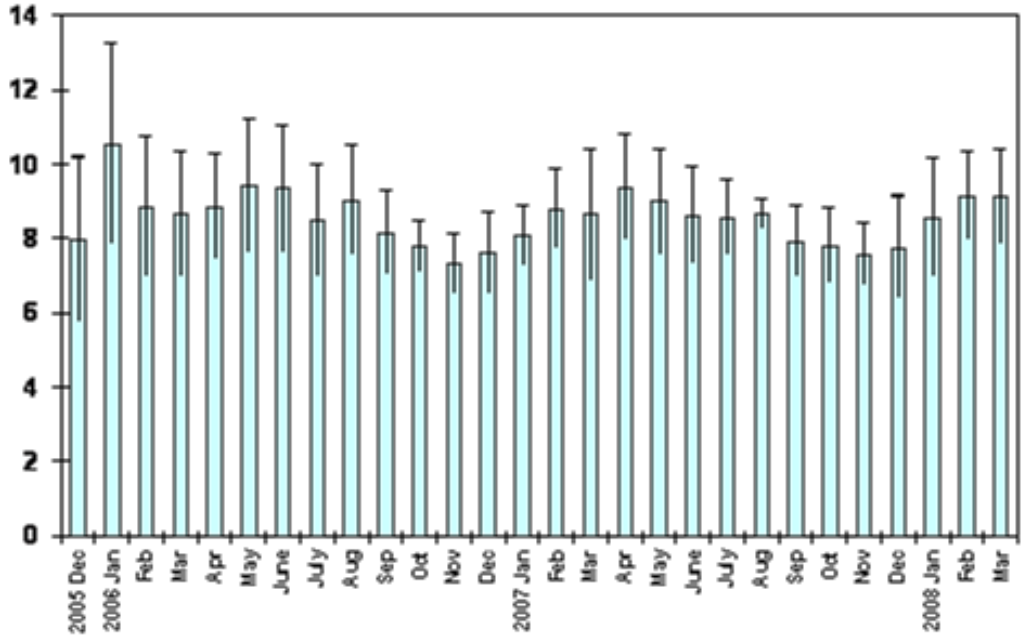

Figure (1): Monthly HbA_{1c}% mean (±SD) throughout the study period. The first three letters of each month represent the months' name during the study period.

Table (1): HbA_{1c}% mean of the season representing months all through the study period, the number of patients (n), and the P value.

Season representing months of the assigned years	Mean HbA_{1c}% (±SD)	n	P value
Decembers - Januaries 2005, 2006, 2007, 2008 Represent autumns	8.52% ± 0.89	113	
Marches - Aprils 2006, 2007 Represent winters	8.87% ± 1.57	111	P <0.001
Junes - Julies 2006, 2007 Represent springs	8.55% ± 0.78	43	
Septembers - Octobers 2006, 2007 Represent summers	7.81% ± 0.94	88	

Table (2): The monthly, and the season representing months' HbA_{1c}% mean in each year separately, the number of patients (n), and the P values.

Year	Month	n	Mean HbA_{1c}%	Mean HbA_{1c}% of season representing months	P value
2005	December	10	7.97 ± 2.2		
2006	January	18	10.53 ± 2.7		
	February	36	8.84 ± 1.9		
	March	27	8.64 ± 1.7	8.75% ± 0.15	
	April	27	8.86 ± 1.4		
	May	20	8.7 ± 1.8		P <0.001
	June	13	8.61 ± 0.59		
	July	10	8.49 ± 1.5		
	August	6	8.42 ± 1.5		
	September	32	8.15 ± 1.1	7.95% ± 0.9	
	October	12	7.76 ± 0.7		
	November	23	7.3 ± 0.8		
	December	14	7.83% ± 0.31		
2007	January	11	8.06 ± 0.81		
	February	18	8.79 ± 1.06		
	March	27	8.64 ± 1.76	9% ± 1.6	
	April	30	9.36 ± 1.42		
	May	25	8.99 ± 1.41		P <0.001
	June	30	8.58 ± 0.04		
	July	17	8,55 ± 1.01		
	August	52	8.66 ± 0.93		
	September	13	7.91 ± 0.95	7.78% ± 0.98	
	October	31	7.79 ± 1.01		
	November	55	7.55 ± 0.83		
	December	24	8.16 ± 0.57		
2008	January	36	8.57 ± 1.59		
	February	42	9.14 ± 1.19		
	March	41	9.11 ± 1.27		

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