Seasonality in Glycosylated Hemoglobin in Normal Subjects

Does Seasonal Incidence in Insulin-Dependent Diabetes Suggest Specific Etiology?

MICHAEL J. MacDONALD, LEONE LISTON, AND IAN CARLSON

SUMMARY

Seasonality in the diagnosis of insulin-dependent diabetes mellitus (IDDM), i.e., increased incidence in winter, was the impetus for this study of seasonality in glycosylated hemoglobin levels in nondiabetics. Glycosylated hemoglobin levels of 35 nondiabetic children and adults were highest at the ends of autumn and winter and lowest at the ends of spring and summer ($P < 10^{-4}$). This result is consistent with reports of seasonal variation in blood glucose, with the highest levels occurring in winter, as well as reports that suggest an internal milieu of increased counterinsulin action in winter due to seasonality in counterinsulin hormones, dietary factors, body weight, amount of exercise, growth rates in children, and ambient temperature. IDDM is caused by the gradual destruction of the pancreatic insulin-producing cells via lymphocytic infiltration—a process that may occur over years. We conclude that a decreased carbohydrate tolerance associated with winter can explain the seasonal variation in the incidence of IDDM and that this seasonality is caused by the precipitation of overt carbohydrate intolerance in individuals with already seriously compromised insulin secretory capacity. This implies that seasonality is not very informative about the cause of the destruction of pancreatic insulin-producing cells.

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The current consensus seems to be that susceptibility to insulin-dependent diabetes mellitus (IDDM) is inherited but that its expression depends on an environmental trigger. Evidence that inheritance is important in causing IDDM comes primarily from studies of identical twins and HLA. Numerous HLA studies have shown that IDDM is associated with certain HLA specificities that are, of course, inherited. When IDDM does occur in monozygotic twins, the concordance is no more than 30–50% (1,2). The fact that concordance does not approach the expected 100% for a strictly genetically determined disorder has been taken as evidence that environmental factors are important in triggering IDDM in genetically susceptible individuals.

The environmental factor most frequently implicated in the seasonal incidence of IDDM has been viral infection. This is largely because of seasonal variation in the diagnosis of IDDM. Numerous reports have described an increased incidence of IDDM during the fall and winter in both the Northern (3,4) and Southern (5,6) Hemispheres. Other studies have found little seasonal variation in incidence (7), and the seasonality in diagnosis is often reversed in families with multiple affected siblings (8). However, results of studies of viral-antibody titers in subjects with recent onset of IDDM have been inconclusive, as have surveys attempting to correlate the incidence of IDDM with outbreaks of viral infection (9).

To obtain more insight into whether the seasonal presentation of IDDM is etiologically important, we measured glycosylated hemoglobin in nondiabetic children and adults during various seasons. We queried whether nondiabetics would show a seasonal variation in average blood sugar that is reflected by a small seasonal variation in the glylcosylated hemoglobin. In accordance with reports of higher blood sugar and counterinsulin hormone levels in nondiabetics in winter, the survey of glycosylated hemoglobin indicated that the average blood sugar level is higher during the autumn and winter. This information supports the hypothesis that the higher rate of diagnosis of IDDM in winter is a nonspecific reflection of increases in factors that are stressful to carbohydrate tolerance in winter.

SUBJECTS AND METHODS

Blood samples were collected in EDTA from 35 nondiabetics (15 subjects were aged 6–15 yr, 9 were 16–21 yr, and 11 were 33–49 yr) within 2 wk of the end of each of the four seasons. The blood was refrigerated until the glycosylated

From the Pediatric Diabetes Program, University of Wisconsin Medical School (M.J.M.), and the Clinical Laboratory, University Hospital (L.L., I.C.), Madison, Wisconsin.

Address correspondence and reprint requests to Dr. Michael J. MacDonald, University of Wisconsin Medical School, 1300 University Avenue, Room 3459, Madison, WI 53706.

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hemoglobin was measured, which was usually within 4 days of obtaining the sample. Glycosylated hemoglobin was determined over an 18-mo span by ion-exchange chromatography with a kit from Bio-Rad and over the span of a year by phenylboronate affinity chromatography with a kit from Isolab (10). At each time of the year, measurements were made on small groups of samples in 5–7 separate assays to minimize the influence of a single assay on the results. The ion-exchange chromatography tests were done in the University of Wisconsin Hospital clinical laboratory. Samples of standard hemolysates were stored at −85°C and were included in the assay each day. Over the 18 mo of testing, the coefficients of variation ranged from 2.3 to 3.9% (N = 27–68 runs per standard hemolysate and >460 runs). The affinity chromatography tests were done in the laboratory of M.J.M. with columns from a single lot. The glycosylated hemoglobin was expressed as a percentage of the total hemoglobin.

Seasonal variation was analyzed by two-way analysis of variance by use of the Minitab statistical package, with season and subject as factors (11). Comparisons of seasonal means were subsequently made by Fisher's least significant difference method. Mean values within each season for males and females were compared by an unpaired t test, and the relationship with age was tested by regression analysis (11). Rank analysis was done with the Friedman rank-sum test (12).

RESULTS

Glycosylated hemoglobin values in the 35 nondiabetic subjects showed marked seasonality ($P < 10^{-4}$), whether measurements were made by ion-exchange chromatography or by the more specific affinity chromatography method (Table 1). Because the measurements were made by two different methods (each with different technical problems) in separate laboratories, and the time spans over which the measurements were made overlapped but were different, the seasonality was probably real and not due to variation in the laboratory methodology. The highest values were recorded at the ends of autumn (December) and winter (March), and the lowest values were found at the ends of spring (June) and summer (September). The autumn and winter values were not significantly different from each other, and the same was true for the spring and summer values. Values from the males (N = 15) and females (N = 20), when analyzed separately, each showed seasonality ($P < .005$), and their means did not differ significantly from each other at any time of the year. There was no significant relationship with age. There was no evidence of skewness in the data. The means were close to the medians; the highest quartile was at the end of winter, and the lowest quartiles were at the ends of spring and summer. Rank analysis confirmed that the highest values were in autumn and winter and the lowest values were in spring and summer ($P < .0001$).

TABLE 1
Average glycosylated hemoglobin values at the end of each season in 35 nondiabetics

	Glycosylated hemoglobin (% of total hemoglobin ± SEM)	
Mo	By affinity chromatography	By ion-exchange chromatography
March		6.9 ± 0.09
September		6.2 ± 0.08*
December	4.1 ± 0.08	6.6 ± 0.09
March	4.3 ± 0.07	
June	3.7 ± 0.07*	6.2 ± 0.08*
September	3.8 ± 0.06†	6.3 ± 0.09†

*$P < .001$ vs. March or December, †$P < .02$ vs. December and $P < .001$ vs. March.

DISCUSSION

The finding that glycosylated hemoglobin levels are higher in winter is consistent with recent reports of seasonal variation of blood sugar in humans (13–15). Glycosylated hemoglobin reflects a subject's average blood glucose in the previous 8–12 wk, and measurements of glycosylated hemoglobin were made near the end of each season. Suarez and Barrett-Connor (14) studied the seasonal variation in fasting plasma glucose levels in 4541 men and women in southern California and found a 0.6-mM (11 mg/dl) average difference between the highest levels in winter and the lowest levels in spring. Jarrett et al. (15) surveyed postprandial blood glucose levels in 3346 subjects aged ≥45 yr in London. Their data show that the highest blood glucose levels occurred in December through February. In addition, Jarrett et al. (15) analyzed data from oral glucose tolerance tests administered to a population of male civil servants aged ≥40 yr living around Whitehall. The average blood glucose levels were highest in winter and lowest in spring. Fahlen et al. (13) administered oral glucose tolerance tests to 100 male subjects <55 yr old who had survived a myocardial infarction and found lower fasting and stimulated blood glucose and insulin values during the summer.

Available evidence indicates that seasonal variation in the levels of counterinsulin hormones occurs and that the level of each hormone is higher in winter than in summer. These hormones include cortisol (16–18), glucagon (19), 17-hydroxycorticosteroids (17,18), and thyroxine (20–22). In many but not all studies of annual rhythms of thyroid function, higher levels of thyroxine and/or thyroid-stimulating hormone were observed in winter (20–25). Presumably this seasonal variation reflects a regulatory effect of hypothalamic function.

Glycogen levels of diaphragm muscle in laboratory mice show a marked seasonal variation, with values in autumn and winter about one-fourth to one-third of those in spring and summer (26). It was hypothesized that seasonal antagonism to insulin is responsible for this variation (26). In the rat heart, sensitivity to insulin is reduced in winter, and it is interesting that a diminution in insulin sensitivity can be produced by a gradual shortening of the day length of artificial light from 12 to 8.5 h over 6 wk, but not by an abrupt change from a 12- to an 8.5-h day (27).

Counterinsulin hormones increase in humans and laboratory animals with exposure to cold temperatures. Plasma triiodothyronine has been shown to be increased in humans in a cold environment (21,25). In cold-adapted rats, plasma glucagon (28), urinary vanillylmandelic acid, food intake, and body weight are increased (29). Gluconeogenesis is increased in cold-adapted rats (29) and is associated with increased (but normal) blood glucose values (30).

Cold may decrease carbohydrate tolerance in humans. Frazier (in ref. 31) reported that during the U.S. Antarctic expedition of 1939–1941, hyperglycemia was frequently observed in members of the party over many weeks of observation. Campbell et al. (32) studied glucose metabolism in Antarctica in 1972 and found significant seasonal differences in glucose tolerance. In oral glucose tolerance tests performed in 12 young men, blood glucose values were lowest in midsummer. Moreover, insulin levels were higher in winter for a given level of blood glucose (33), which suggests insulin resistance in winter.

In humans, seasonal differences in diet and exercise may influence blood glucose. Exercise increases insulin sensitivity (34), and overweight is correlated with decreased insulin sensitivity. In their study of plasma glucose in humans, Suarez and Barrett-Connor (14) noticed that a history of recent weight gain corresponded to the season of maximum fasting plasma glucose, which was winter as was mentioned above. Measurements by Zahorska-Markiewicz and Markiewicz (35) in Poland indicated that physical fitness is higher in summer, that fat is the main fuel in winter, and that carbohydrate is the main fuel in summer, as judged by the respiratory quotient. The efficiency of weight loss by dietary restriction in obese women was season dependent, with the most marked weight loss in spring and the worst results in winter (36).

Growth and sexual maturation seem to be associated with an unfavorable effect on carbohydrate tolerance, as judged by the increased insulin requirements in diabetic children occurring around the pubertal growth spurt, as well as by an increased incidence of diabetes occurring around the age of puberty (3,9). Marshall (37) has shown that children grow faster in the 3 or 6 mo growth periods ending in March and June, respectively, indicating that growth rates are highest in winter.

Glycosylated hemoglobin values fluctuate over a wider range in diabetics than in nondiabetics. Mortensen et al. (38) reported that glycosylated hemoglobin values in diabetic children in Sweden are lowest in summer and suggested that this is in accordance with the better regulation of the disease seen during the summer. It seems likely that the higher glycosylated hemoglobin levels in diabetic children in winter may reflect unfavorable effects of winter on eating and exercise behavior as well as more direct intrinsic season-related effects on carbohydrate metabolism.

In summary, humans are apparently more hyperglycemic in the winter than in the summer, which may be due to more stresses to carbohydrate tolerance in the winter. IDDM is caused by an immunologically mediated destruction of the pancreatic β-cells, and probably >90% of the β-cell mass must be lost before insulin deficiency is clinically apparent (39). When the number of β-cells is markedly decreased and near the borderline at which insulin deficiency occurs, the stresses to carbohydrate tolerance associated with winter could unmask diabetes. A scenario can be imagined in which the failing β-cell is unable to respond to the increased insulin requirement brought on by an internal milieu of increased counterinsulin hormones, increased growth and weight brought on by autumn and winter (perhaps due to fewer hours of daylight and colder temperature), and alterations in diet and decreased activity that may result from winter and colder temperatures. Such a scenario might be a more plausible explanation for the increased frequency of diagnosis of IDDM during the autumn, winter, and early spring rather than acute infection stimulating destruction of β-cells either directly or via an immunologic mechanism. In view of evidence that immune destruction of the β-cell can begin years before the clinical presentation of IDDM (40), it seems more likely that if a specific infectious insult is involved in causing IDDM, it frequently occurs years before the clinical onset of IDDM. It is also quite possible that the sum of several nonspecific environmental factors determine which genetically susceptible individuals will show overt IDDM.

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