Diabetes in the Seneca Indians
Plasma Insulin Responses to Oral Carbohydrate

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SUMMARY

In a group of adult Seneca Indians living in Western New York, 14 per cent were discovered to have previously diagnosed diabetes, and 20 per cent of the remainder had a plasma glucose of 200 mg. per 100 ml. or greater one hour after oral carbohydrate. This report describes the glucose and insulin responses to oral carbohydrate in fifty of these subjects who were not previously known to have diabetes during initial testing.

On the basis of the results of a two-hour oral glucose tolerance test, forty-six subjects were classified into "diabetic" or "normal" categories. Four persons formed an intermediate group. The diabetics differed from the normals in that (1) they were older and more obese, though even the normal population was significantly obese, and (2) the mean fasting plasma insulin level was three times greater and the insulin response to oral glucose two and one-half times greater than in normals. When diabetics were subdivided on the basis of obesity or degree of glucose intolerance, no significant differences in insulin secretion could be detected. A group of diabetic subjects with a degree of obesity comparable to that of normal subjects still demonstrated two-fold increases in both fasting and postglucose insulin levels.

The elevated insulin levels of diabetics can be explained only in part by co-existent obesity and suggest the presence of insulin resistance associated with diabetes in these Indians. DIABETES *18*:38-43, January, 1969.

A high prevalence of diabetes mellitus has been reported to exist in several groups of North American Indians. These have included the Pimas,[1] the Oklahoma Seminoles,[2] the Alabama Coushattas,[3] and the North Carolina Cherokees.[4]

A recent survey of Seneca Indians has also shown a high prevalence of diabetes.[5] Fourteen per cent of a group of 221 systematically selected adults were found to have previously diagnosed diabetes, and 20 per cent of the remainder had a plasma glucose concentration of 200 mg. per 100 ml. or greater one hour after 75 gm. of a partially hydrolyzed carbohydrate drink.

The Seneca Indians were the largest subdivision of the Iroquois Confederation, which at one time occupied most of what is now New York State. Today about 2,500 Senecas live on the Cattaraugus Reservation in Southwestern New York. Pedigree information and blood grouping data suggest considerable racial intermixture.[6] Two thirds of the Senecas do not specifically admit to the knowledge of white ancestors, however, and identity as Indians is clearly maintained.

The present study compares fasting plasma insulin levels and the insulin secretory response to oral glucose stimulation between two groups of Seneca Indians distinguished by their plasma glucose responses to oral carbohydrate.

METHODS

A group of fifty Senecas, none of whom was known to have diabetes prior to the initial survey,[5] were subjected to a two-hour oral glucose tolerance test. Subjects were selected on the basis of their plasma glucose values during the initial survey.

Twenty-four had had plasma glucose values greater than 200 mg. per 100 ml. whereas the remainder had had values of less than 160 mg. per 100 ml. They were instructed to consume their normal diet* prior to the test and to arrive at the clinic on the morning of the test after an overnight fast. After a fasting blood sample was obtained, each subject was given 75 gm. of carbohydrate orally, as Dexcola.† Additional blood samples were obtained at 30, 60, 90 and 120 min., immediately chilled, and the plasma separated within five hours.

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*The Seneca diet appears to be similar to the usual American diet. Food is purchased off the reservation and is prepared in conventional fashion. Detailed dietary history was not obtained in the subjects of the present study.

†Custom Laboratories Inc., Baltimore, Maryland.

Potassium oxylate and sodium fluoride were added to the samples on which glucose measurements were to be performed, and heparin was added to the samples used for insulin determination. Plasma glucose was measured by the AutoAnalyzer ferricyanide method.[7]

In this study, subjects with decreased carbohydrate tolerance were termed "diabetic" if two or more plasma glucose values exceeded the following limits:[8]

Time	Plasma glucose, mg. per 100 ml.
Fasting	115
30 minutes	195
60 minutes	185
90 minutes	160
120 minutes	140.

Subjects with all glucose values within the above limits were considered "normal." An intermediate category was established for those individuals with only one glucose value exceeding the above limits.

Insulin was measured on duplicate aliquots from each sample by a double antibody radioimmunoassay, the details of which have been previously described.[9] Insulin levels in fasting samples of all subjects were redetermined in duplicate at a later time. The coefficient of variation between the duplicates within this assay was 5.9 per cent. The coefficient of variation between the pairs of fasting values determined on different days was 20 per cent.

The degree of hyperglycemia ($\triangle$G) was estimated by calculating the area circumscribed by the glucose curve. This was defined by a plot of plasma glucose values at the various time intervals from 0 to 120 min. after glucose, with the fasting glucose value being used as a base. Insulin secretion in response to glucose loading ($\triangle$I) was estimated in an identical manner. An insulinogenic index was calculated according to the method of Seltzer et al.[10] using the ratio of $\triangle I/\triangle G$. Statistical analyses were performed according to Snedecor.[11]

An estimate of obesity was made both by calculating the ponderal index, defined as the height in inches divided by the cube root of the weight in pounds[12] and by expressing an individual's weight as a per cent of ideal weight.[13]

RESULTS

Characteristics of "diabetics" and "normals"

Twenty-three subjects exhibited "diabetic" glucose tolerance tests and an identical number had "normal" glucose tolerance tests. Four subjects had a single abnormal glucose value and were excluded from both groups. Data pertaining to these four subjects are included only for correlations involving the entire population. Pertinent comparisons of diabetics and normals are shown in table 1. The diabetics were significantly older than the normals. They were also more obese, as judged by either the ponderal index or the per cent ideal weight. Even the normal population, however, exhibited a significant degree of obesity ($p < .001$) when compared to ideal weight tables derived from a non-Indian population. The two parameters were closely correlated in this population ($r = -.953$) as is shown in figure 1. There

TABLE 1

Comparison of "diabetic" and "normal" Seneca Indians

	Normal (23)	Diabetic (23)	p
Age, years Range	42 ± 3* 26 — 71	59 ± 3 28 — 80	<.001
Sex	13 F 10 M	16 F 7 M	NS†
Ponderal index‡	12.28 ± .11	11.86 ± .18	<.05
Per cent ideal weight‡	115.3 ± 3.3	130.3 ± 5.6	<.05
Fasting plasma insulin, μU./ml.	8 ± 1	24 ± 3	<.001
Insulin response to carbohydrate ($\triangle$I), μU.-min./ml.	5,522 ± 819	13,270 ± 1,819	<.001
Plasma glucose response ($\triangle$G), mg.-min./100 ml.	3,056 ± 391	10,548 ± 592	<.001
Insulinogenic index ($\triangle I/\triangle G$)	2.04 ± .26	1.34 ± .22	<.05

*Mean ± standard error
†Not significant
‡Accurate height and weight measurements were available on twenty-one normals and nineteen diabetics

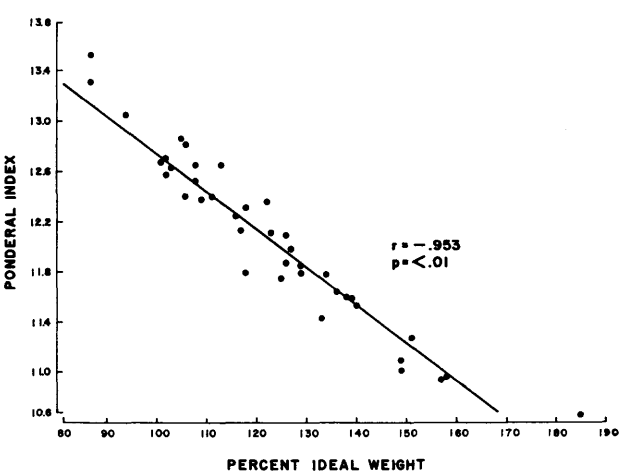

FIG. 1. Correlation of ponderal index (height in inches/$\sqrt[3]{\text{weight in pounds}}$) and per cent ideal weight among the Seneca Indians in whom glucose tolerance tests were performed.

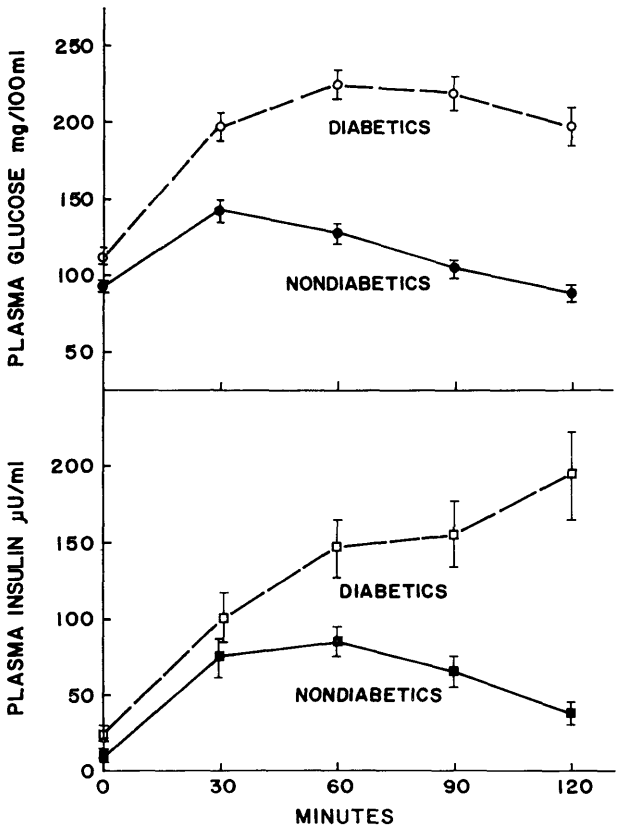

FIG. 2. Comparison of plasma glucose and insulin values in diabetic (n = 23) and nondiabetic (n = 23) Seneca Indians in response to 75 gm. partially hydrolyzed carbohydrate. Shown are the means ± standard error.

was no significant sex difference between diabetics and normals. Fasting insulin values, insulin responses (△I) and insulinogenic indices (△I/△G) are shown in table 1. The diabetics had higher fasting insulin values and a greater absolute insulin response to glucose as determined by △I and by the values at 30, 60, 90, and 120 min. after the carbohydrate drink (figure 2). Despite the elevated insulin levels, the mean insulinogenic index of the diabetics was less than that of the normals. Four diabetic individuals, however, had indices which exceeded the mean index of the normals.

TABLE 2

Correlations among "diabetic" and "normal" Seneca Indians

Variables	Normal		Diabetic	
	r	p	r	p
Ponderal index vs △ I	−.516	<.05	−.145	NS*
Ponderal index vs △ G	−.228	NS	+.054	NS
Ponderal index vs fasting insulin	−.156	NS	−.267	NS
Fasting insulin vs △ I	+.531†	<.01	+.301	NS
Ponderal index vs △ I/ △ G	−.368	NS	−.287	NS
Age vs △ G	.051	NS	−.137	NS

*Not significant
†Partial correlation coefficient with ponderal index held constant: r = +.532, p <.05

Influence of obesity on insulin secretion and carbohydrate intolerance

Because of the recognized effects of obesity on insulin secretion and the high prevalence of obesity

TABLE 3

Comparison of "diabetic" Seneca Indian groups based on obesity and degree of glucose intolerance

	Relative obesity			Degree of glucose intolerance		
	Obese (9)*	Nonobese (10)*	p	Mild (13)‡	Moderate (10)§	p
Age, years	51 ± 5	60 ± 4	NS†	54 ± 5	62 ± 3	NS
Ponderal index	11.20 ± .11	12.46 ± .14	<.001	11.86 ± .28	11.87 ± .23	NS
Plasma glucose response (△G), mg.-min./100 ml.	10,202 ± 943	10,904 ± 954	NS	8,478 ± 368	13,089 ± 503	<.001
Fasting plasma insulin, μU./ml.	27 ± 6	20 ± 4	NS	20 ± 4	28 ± 5	NS
Insulin response to carbohydrate (△I), μU.-min./ml.	14,393 ± 2,883	11,762 ± 2,457	NS	15,650 ± 2,817	10,651 ± 2,274	NS
Insulinogenic index (△I/ △G)	1.71 ± .46	1.01 ± .18	NS	1.71 ± .34	0.85 ± .18	NS

*Accurate height and weight measurements were available on only nineteen diabetics
†Not significant
‡Defined as △G less than 10,000 mg.-min./100 ml.
§Defined as △G greater than 10,000 mg.-min./100 ml.

among the Senecas, an attempt was made to evaluate the influence of obesity on carbohydrate intolerance. The effects of obesity were examined in several ways. In the normals the insulin response to glucose correlated with the degree of obesity and with the fasting insulin value (table 2). Correlation coefficients varied by no more than .02 when per cent ideal weight was substituted for ponderal index. A very slight correlation was present between the fasting insulin and the ponderal index in the entire population, but not in either group alone. Among diabetics, the degree of glucose intolerance did not correlate with either the degree of obesity, age, or the magnitude of the insulin response. The insulinogenic index did not correlate with the degree of obesity in either the diabetics or normals.

To examine further the effect of obesity within the diabetic group, the population was divided into two groups using as a basis, the ponderal index. The non-obese group had a mean ponderal index of 12.46 (mean per cent ideal weight: 112) whereas that of the obese group was 11.20 (mean per cent ideal weight: 150). The degree of glucose intolerance was similar in the two groups. Insulin values, both fasting and after glucose, and the insulinogenic index were slightly but not significantly greater in the obese diabetics (table 3). Conversely, when the diabetics were divided into two groups on the basis of the degree of glucose intolerance ($\triangle G$), no significant differences were present with respect to age, ponderal index, fasting insulin levels, insulin response to glucose, or the insulinogenic index (table 3). The rise of plasma insulin after glucose was equally rapid in the two groups. When normals were further subdivided into two equal groups based on the ponderal index, no significant correlations between the variables listed in table 2 were present in either subgroup.

Finally, to compare groups of diabetics and normals with similar degrees of obesity, the most obese diabetics were excluded sequentially until the ponderal index (and per cent ideal weight) of the diabetics was identical with that of the normals (table 4). The variances and the distribution patterns of the two groups were also quite similar. The diabetics, however, still exhibited a mean fasting insulin level two and one-half times as great and an insulin response to glucose twice as great as the normals (see figure 3). The insulinogenic index was decreased by one half in the diabetics despite the elevated insulin levels. These differences were all highly significant. Among this group of diabetics, fasting insulin levels correlated with the insulin response to glucose ($r = +.609$, $p < .05$) but not with fasting glucose or the insulinogenic index.

TABLE 4

Comparison of "normal" and obesity-matched "diabetic" Seneca Indians

	Normals (23)	Obesity-matched diabetics (13)	p
Ponderal index	12.28 ± .11	12.29 ± .15	
Per cent ideal weight	115	117	
Fasting plasma insulin, μU./ml.	8 ±1	20 ± 3	<.001
Insulin response to carbohydrate ($\triangle$I), μU.-min./ml.	5,522 ± 819	11,117 ± 1,917	<.01
Plasma glucose response ($\triangle$G), mg.-min./100 ml.	3,056 ± 391	11,000 ± 602	<.001
Insulinogenic index ($\triangle$I/$\triangle$G)	2.04 ± .26	1.00 ± .18	<.01

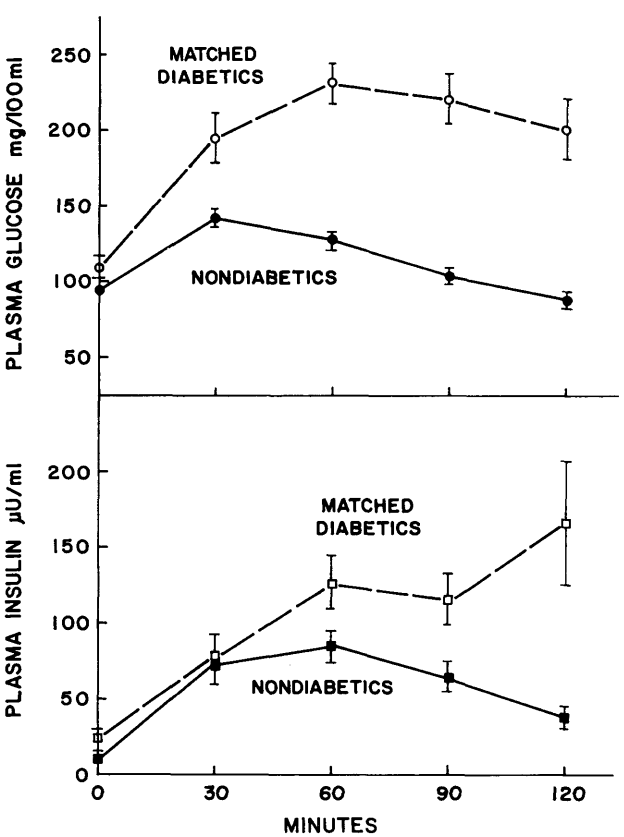

FIG. 3. Comparison of plasma glucose and insulin values in diabetic Seneca Indians (n = 13) matched to a comparable degree of obesity with nondiabetics (n = 23).

DISCUSSION

The results of the present study would appear to indicate that "diabetic" Seneca Indians have higher fasting insulin levels and a greater insulin response to oral carbohydrate than the "normal" Indians. Certain characteristics of the population, however, require comment.

First, the diabetic Senecas were older than the normals. Since no correlation existed within either the diabetic or normal group between age and the degree of glucose intolerance, the difference in age is not likely to account fully for the difference in insulin secretion. Second, the diabetic Senecas were more obese than the normals, even though the latter were also obese, as judged by standard criteria.[13] Since obesity, per se, is associated with increased insulin levels,[14] a valid comparison between diabetics and normals required that the degree of obesity be comparable. When such a comparison was performed, elevated insulin levels persisted in the diabetic group. This observation suggests that a resistance or insensitivity to insulin action exists among the diabetics beyond that which is attributable to obesity. This is supported by the presence of a significant correlation between the degree of obesity and the insulin response in normals and its absence among diabetics. A study of glucose utilization rates is being planned in an attempt to confirm this impression.

The insulinogenic index[10] was evaluated with respect to its usefulness in assessing insulin secretion. The mean index of the normal population was identical to that observed by Seltzer et al.[10] in mild diabetics and less than half of the value they observed in normals. In addition, the insulin secretory response of the diabetics was twice while the insulinogenic index was only half that of the normals with comparable obesity. The limited value of the insulinogenic index is related to the complex relationship between $\triangle$I and $\triangle$G. The latter parameter reflects not only the stimulus for insulin secretion, but also the effectiveness of the secreted insulin. Consequently, a change in the ratio could be the result of either phenomenon, alone or in combination. Interpretation of the reduced insulinogenic index of the diabetics in this study, therefore, is difficult but consistent with the presence of insulin insensitivity.

The existence of hyperinsulinemia in maturity-onset diabetes has been reported by other workers. Kreisberg et al.[15] reported that among a group of obese subjects, those with diabetic glucose tolerance tests had significantly greater fasting insulin levels and insulin responses to glucose. Paulsen et al.[16] in a study of insulin secretion among obese children reported a greater response among those individuals with a positive family history of diabetes. These observations suggest that a degree of insulin insensitivity exists in those individuals with a genetic predisposition toward diabetes. In a study which is in many ways comparable to the present report, Genuth et al.[17] reported a greater insulin response to glucose among obese diabetic Pima Indians than among obese nondiabetic controls. In contrast to these studies, are the well documented reports by Seltzer et al.[10] and by Perley and Kipnis[18] of relative insulinopenia among maturity-onset diabetics when compared with controls of comparable degrees of obesity. Of even greater interest is a recent report by Rimoin and Saiki[19] describing the insulin response of Navaho Indians. Although the Navahos, like the Pimas and the Senecas, are obese, the prevalence of diabetes is much lower than in either of the other groups. In addition, the insulin responses of the mildly diabetic Navahos were identical to that of the controls while the more severe diabetics exhibited a true insulinopenia.

Several possible explanations exist for a discrepancy between these divergent observations. First, the stage and perhaps duration of diabetes may have been different. The present report and that of Genuth et al.[17] were performed in subjects only discovered to have diabetes shortly before the studies were performed. The study of Paulsen et al.[16] described subjects with normal glucose tolerance and with only a positive family history of diabetes. It is conceivable that the increased insulin response seen at this stage does not persist and that studies demonstrating insulinopenia involved subjects with diabetes of a longer duration. It may also be important to note that four studies, including the present report, showing an increased insulin secretion in diabetics or prediabetics, all utilized an obese population. It is certainly possible that the pathogenetic mechanisms associated with obesity related diabetes are different from those associated with diabetes in the nonobese. The observations of Saiki and Rimoin,[19] however, are not consistent with this hypothesis.

Since the prevalence of diabetes is so much higher in certain Indian tribes than in the non-Indian population, the question must be raised as to whether a different pathogenetic basis exists for the disease. The Seneca diabetics do show evidence of diabetic vascular disease (unpublished observations) but the incidence of juvenile-onset and ketosis-prone diabetes is low.[5] Inasmuch as a similar pattern of increased insulin secretion has

been reported in non-Indian diabetics, the present observations provide no evidence of a difference in pathogenesis.

The present studies do not indicate the sequence of events which precede the development of diabetes. They do, however, imply that if relative insulinopenia does occur, it is a late phenomenon which is preceded by a period of hyperinsulinemia. Further studies in this population will be required to determine the temporal relationships between obesity, hyperinsulinemia, and diabetes.

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