Reduced Glucose Tolerance in Elderly Human Subjects

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SUMMARY

The high incidence of "abnormal" oral glucose tolerance tests in "normal" subjects over seventy years of age has been confirmed: 77 per cent in this series of individuals. Calculation of glucose disposal rates (GDR's) after three successive intravenous injections of glucose (25 gm.) in fifteen elderly normal subjects revealed GDR's which rose with successive injections, and which were significantly inferior to those observed in young adult normal subjects, yet significantly superior to the findings in patients with tolbutamide-responsive diabetes mellitus. Serum levels of insulin-like activity (ILA) assayed on the rat epididymal fat pad were higher in the elderly than in the young normal subjects both in the fasting state and after the first and third glucose injections. It is concluded that the abnormal tolerance of elderly subjects to an oral load of glucose is not due to retarded absorption of the administered glucose nor to impaired pancreatic secretion of insulin, but presumably results from a higher level of circulating insulin antagonist or from some other cause of delayed glucose uptake from the plasma. The present difficulties in diagnosing diabetes in elderly subjects have been pointed out, and possible means of differentiating between normal and diabetic individuals at all ages have been discussed. DIABETES *14*:579-83, September 1965.

Glucose tolerance in elderly nondiabetic individuals has been the subject of several recent studies.[1-10] The general finding has been that elderly subjects frequently show a mild defect in glucose tolerance. In an attempt to compare the pancreatic insulin-secreting capacity of normal and diabetic subjects, Streeten, Gerstein, Woolfolk and Doisy[11] have studied the responses to three successive intravenous loads of 50 per cent glucose solution. From the observed decline of the plasma glucose concentration after each injection, the rate at which glucose disappeared from the extracellular fluid (Glucose Disposal Rate, GDR) was calculated, essentially as described by Moorhouse, Grahame and Rosen.[12] In normal young adult subjects studied by this method, the GDR was found to average 17.40 gm./35 min. after the first injection of glucose and invariably to increase after the second and third injections of glucose (mean GDR 21.66 and 23.43 respectively). From measurements of plasma insulin-like activity (ILA) and from observation of the effects of injecting increasing doses of Crystalline Insulin with the three loads of glucose, it was concluded that the progressive enhancement of the GDR probably resulted from the release of increasing amounts of insulin from the pancreas after successive glucose injections.

In the present study, the frequent occurrence of diabetic oral glucose tolerance tests in elderly "normal" subjects has been confirmed. The mechanism of this abnormality has been explored by comparing the GDR's and the plasma ILA levels after three successive intravenous injections of glucose (25 gm.) in groups of young and elderly "normal" subjects.

METHODS AND MATERIALS

Fifteen elderly subjects (five male, ten female) in a county home for the elderly were selected for study. The subjects were at least seventy years of age, had had no glycosuria or elevated fasting blood sugars in the past, had no known family history of diabetes mellitus and showed no clinical or laboratory evidence of renal, cardiovascular or endocrine disease, or of active infections. The subjects were not confined to bed or restricted in their activities which were considered to be approximately normal for their age. Twenty-three normal, young adults who were studied over the same period of time were healthy physicians, medical students, nurses and laboratory technicians without a family history of diabetes. Each subject was prepared for three days prior to testing with a diet containing 300 gm. of carbohydrate daily.[13] All tests were started between 8 and 9:15 a.m., after an overnight fast.

The patient was instructed to void immediately be-

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fore the study started. A fasting blood specimen was drawn, and then 50 ml. of 50 per cent glucose solution was injected intravenously over a four-minute period. Blood specimens were taken through an indwelling needle in a vein in the other arm, ten minutes after the start of the injection, and at five-minute intervals thereafter, for a total of six post-injection samples. A urine specimen was then obtained thirty-five minutes after the beginning of the glucose injection. The entire procedure, including glucose injection, withdrawal of blood samples, and collection of urine, was repeated twice, starting forty and eighty minutes after the beginning of the initial glucose injection.

Blood specimens were placed in tubes containing 20 mg. potassium oxalate and 25 mg. sodium fluoride. Plasma (undiluted) and urine (diluted 1:20) were analyzed for glucose concentrations by a standard ferro-ferricyanide method, using the AutoAnalyzer (Technicon).

Glucose disposal rate, GDR, was calculated as described elsewhere.[11] Essentially, this involved calculation of the regression of the line representing the semilogarithmic decline of plasma glucose concentration with time after each glucose injection. After correcting for the effects of glycosuria on the plasma glucose concentration, the fall in plasma glucose concentration over 35 min. was multiplied by the glucose space to give the GDR in gm./35 min.

Additional samples of blood, drawn at zero time and twenty minutes following each injection, were kept on ice and assayed for insulin-like activity using the rat epididymal fat pad.[14] Several days, usually at least a week after the intravenous test, a standard oral glucose tolerance test was performed, using 100 gm. glucose, in thirteen of the fifteen elderly subjects studied.

RESULTS

The results of the oral glucose tolerance tests are shown in table 1. Of the thirteen elderly patients on whom the oral tests were performed, ten (77 per cent) were abnormal according to the criteria of Fajans and Conn,[15] since the blood sugar peak exceeded 160 mg. per 100 ml., while the blood sugars at one and one-half and two hours after the glucose load were above 140 and 120 mg. per 100 ml. respectively. One of these ten subjects (A.L.) had severely diabetic glucose tolerance, as shown by both the oral and the intravenous tests.

The calculated glucose disposal rates in the elderly subjects are shown in table 2, and the means of these results are compared in the table with the means obtained by the same methods in twenty-three young subjects (less than thirty years of age).[11] It is evident that in the elderly individuals the GDR, after the first injection of glucose, was considerably and significantly lower ($P < .001$) than in the young subjects by Student's t test. After the second and third injections of glucose this difference in GDR was smaller but still significant ($P < .001$).

TABLE 1

Blood glucose concentrations (mg. per 100 ml.) during oral glucose tolerance tests in thirteen elderly normal subjects

	Time in Minutes					
Subjects	0	30	60	90	120	180
T.K.	84	118	122	126	116	106
P.K.	88	134	162	130	108	96
T.M.	76	134	172	176	162	128
C.W.	78	146	170	164	154	74
C.S.	84	136	180	180	182	122
J.W.	80	130	136	160	148	106
M.R.	90	154	192	172	152	102
C.M.	78	154	198	188	168	116
S.A.	90	158	184	188	192	196
M.M.	84	144	214	222	228	162
B.M.	96	118	102	104	92	118
A.S.	106	148	210	142	132	70
A.L.	110	202	344	312	280	142
Mean	88.0	144.3	185.1	174.2	162.5	118.3

Comparison of insulin-like activity (ILA) in the elderly and young normal subjects, measured at corresponding intervals in both groups, showed (table 2) that the mean fasting level of serum ILA was higher (though not significantly so) in the elderly than in the young adult subjects. The serum ILA concentrations rose significantly above fasting levels after the second and third glucose injections ($P < .05$) in the young adults and after all three injections in the elderly subjects ($P < .05$). These glucose-induced rises in ILA were usually considerably higher in the elderly subjects than the corresponding elevations of ILA concentrations in the young normal individuals with the mean differences in plasma ILA levels between the young and the elderly normal subjects statistically significant after the first and third injections of glucose ($P < .001$ and $P < .05$). Table 3 shows that the maximal increase in serum ILA level after any of the glucose injections was significantly greater in the elderly than in the young adult subjects studied ($P < .001$).

DISCUSSION

The results of this study have confirmed the finding[1-3,7-10] that a large percentage of elderly individuals in apparently good health, have "diabetic" glucose tolerance curves by the oral method, employing 100 gm. of glucose. Thus the finding in this study that 77 per cent of thirteen apparently healthy subjects over seventy

TABLE 2

Glucose disposal rates (GDR in gm./35 min.) and serum concentrations of ILA (μU./ml.) fasting and at 20 min. after each intravenous injection of glucose

Subject	Sex	Age	Glucose disposal rates* I	II	III	Serum ILA 0	I	II	III
T.K.	M	70	14.7	16.6	18.9	240	148	535	1,050
P.K.	M	77	19.4	20.1	21.1	173	251	362	535
T.M.	M	81	13.1	18.7	23.8	269	489	385	354
C.T.	M	73	8.5	4.8	15.5	162	169	155	223
C.W.	M	74	12.2	16.0	15.0	575	1,260	525	870
C.S.	F	84	7.1	12.9	17.7	186	234	228	660
J.W.	F	87	8.7	18.5	22.3	195	550	397	478
M.R.	F	88	9.9	18.8	17.1	397	426	—	955
C.M.	F	84	4.8	14.5	19.2	186	380	214	148
S.A.	F	83	12.9	16.9	19.7	630	500	478	775
M.M.	F	92	13.1	14.3	15.5	488	525	600	720
J.K.	F	82	8.2	15.3	19.0	330	223	228	525
B.M.	F	91	10.3	11.3	19.2	190	335	263	295
A.S.	F	80	17.6	19.6	24.0	251	478	375	560
A.L.	F	76	8.1	16.0	22.0	316	295	354	308
Mean (elderly)		81.5	11.24	15.62	19.35	305.9	417.5	364.2	563.7
S.E.M.			1.04	1.01	0.75	39.4	23.7	24.5	70.4
Mean (young normal) subjects		25.8	17.40	21.66	23.43	230.9	261.0	295.7	322.0
S.E.M.			.62	.52	.65	27.6	16.3	29.7	21.5
n			23	23	23	8	8	8	8
p			<.001	<.001	<.001	>.1	<.001	>.2	<.05

* These GDR's have been reported elsewhere[11] and are reproduced here with the permission of the Editor, "Journal of Clinical Endocrinology and Metabolism."

TABLE 3

Serum ILA: Fasting and maximal postglucose levels

	Fasting ILA (μU./ml.) Mean ± S.E.M.	Max. ILA after Glucose (μU./ml.) Mean ± S.E.M.	P
Young adults	230.9 ± 27.6	342.1 ± 15.0	<.001
Elderly adults	305.9 ± 39.4	624.7 ± 177.2	<.001
P	N. S.	<.001	

years of age had "diabetes" by conventional criteria for the oral glucose tolerance test is in good agreement with the incidences reported by Spence[1] (60 per cent), Marshall[2] (53 per cent), Chesrow et al.[7] (53 per cent), Brandt[9] (75 per cent), and Gottfried et al.[10] (100 per cent).

Since the mean GDR following the first glucose injection by the intravenous route was also significantly below the mean result obtained in young normals, the abnormal oral glucose tolerance in the elderly is not simply the result of abnormal absorption of glucose from the gastrointestinal tract. These results with the intravenous glucose tolerance test confirm the findings of Schneeberg et al.[6] and Silverstone et al.[16] in elderly individuals.

After successive intravenous loads of glucose, the GDR was found to increase progressively in the elderly subjects in a manner qualitatively comparable and quantitatively superior to the findings in the young normal subjects. The GDR in the elderly subjects was significantly greater after each of the three glucose injections than those measured in a group of tolbutamide-responsive diabetics.[11] Moreover, the GDR's in the elderly subjects, though lower than those recorded in young normal subjects, were associated with plasma levels of ILA which were usually higher than those found in the younger subjects. The lower GDR's in the elderly subjects cannot, therefore, be attributed either to lower levels of pancreatic insulin secretion in the fasting state or to reduced islet-cell responses to the physiological stimulus of hyperglycemia. The reduced GDR's in elderly subjects may, therefore, have resulted from antagonism to the action of insulin either by a circulating agent[17] or by a substance acting at the cellular level.

Since it is common clinical practice to base the diagnosis of diabetes on the results of oral or intravenous glucose tolerance tests, two possible clinical implications arise from the high incidence of "diabetic" glucose tolerance curves in elderly subjects. First, it might be concluded that almost all human subjects develop diabetes mellitus with advancing years. The inheritance of

diabetes would then be considered to be inheritance of reduced glucose tolerance *before* old age. This interpretation would make it necessary to consider diabetes mellitus not as a distinct disease entity but as part of the aging process which occurs prematurely in many individuals. The demonstration that after successive loads of glucose the mean glucose disposal rate in the elderly subjects remained significantly higher than in the "tolbutamide-responsive diabetics," however, indicates that elderly subjects can be differentiated from "diabetics" as a *group,* even though considerable overlap exists between the two groups of individuals (compare table 2 of this publication with table 4, Streeten et al.[11]). This overlap is the basis of the second possible clinical implication of these data. If, as seems likely, elderly subjects are not almost all (i.e., 77 per cent in the present study) diabetic, then at least it must be admitted that conventional criteria for the diagnosis of diabetes by the glucose tolerance test, performed either by mouth or by the intravenous route, cannot be satisfactorily used to diagnose diabetes mellitus in elderly subjects.

This conclusion is supported by figure 1, in which are plotted the levels of blood sugar two hours after an oral glucose load in the thirteen subjects reported in the present series and in the fifty-two "normal" subjects studied by Brandt.[9] The points enclosed in squares represent the mean two-hour blood sugars of all individuals within each age decade from fifty to eighty-nine years. It is evident that the mean level of the blood sugar two hours after an oral load of glucose rises strikingly with advancing age, at least from 50-59 to 70-79 yrs. In the face of the obviously wide scatter of two-hour blood sugar values, any separation of "normal" from "diabetic" results would be entirely arbitrary and could not be substantiated by independent diagnostic criteria of diabetes at present.

The computed values of the specific rate constant for glucose utilization (k) after intravenous glucose loads (25 gm.) in the thirty females and thirty-five males of various ages, reported by Silverstone and his colleagues[16,18] and in the thirty-eight normal subjects reported by Streeten et al.[11] are shown in figure 2. When these values of K were compared with the rate constants determined in fifteen diabetics in whom the effects of glycosuria were allowed for,[11] the best separation between the diabetic and the normal subjects was made by the line depicted, which joins K values of 1.0 per cent/min. at 20 yrs. to 0.5 per cent/min. at 90 yrs. This arbitrarily drawn line separates all but two of the 103 "normal" subjects between 20 and 90 yrs. of age from fourteen of the fifteen diabetics, all of whom had fasting blood sugars well above 120 mg. per 100 ml., when untreated. It is recognized that there might have been considerably more overlap between the two groups if diabetics with normal fasting blood sugars had been included in the observations. However, the predicament has to be appreciated that there is no way of defining the normal limits of the glucose tolerance test at various

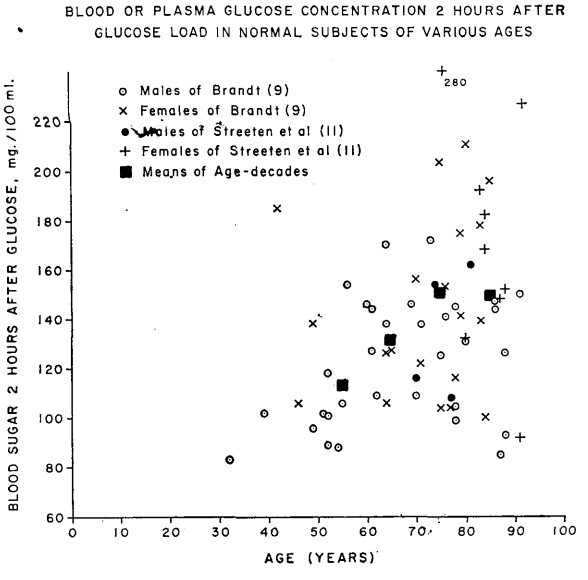

FIG. 1. Blood or plasma glucose concentration two hours after oral glucose load in normal subjects of various ages, reported in the literature.[9,11] The squares represent mean glucose concentrations in all individuals within each age decade (50-59, 60-69 etc.).

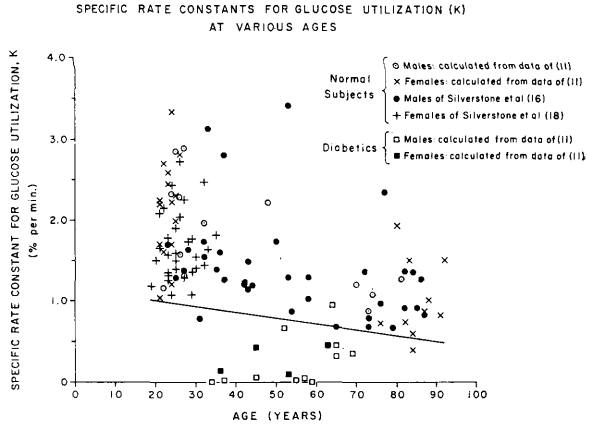

FIG. 2. Specific rate constant for glucose utilization (K) in "normal" individuals of various ages, reported in or calculated from the literature[11,17,18] and compared with K values in fifteen diabetics who had fasting hyperglycemia when untreated.[11] The arbitrarily drawn line, joining K values of 1.0 per cent per minute at twenty years with 0.5 per cent per minute at ninety years separates 102 of the 103 "normal" subjects from fourteen of the fifteen diabetics.

ages except by the empirical method used here and that there is no independent method of deciding whether or not an individual with a given degree of glucose intolerance at any age actually has diabetes. The number of diabetics studied was too small to establish that patients with diabetes mellitus invariably have impaired intravenous glucose tolerance, when compared with "normal" subjects of the same age. However, the fact that fourteen of the fifteen diabetic subjects had k values below the "normal" limits depicted in figure 2 would encourage further studies on patients with diabetes, to determine the reliability of these or similar diagnostic criteria for diabetes in adults of all ages.

The findings of these and similar studies lead to the conclusion that glucose tolerance tests are of limited value in the recognition of diabetes mellitus in elderly individuals at present, except in those instances in which gross glucose intolerance is revealed, since, (1) there are no generally acceptable criteria for interpreting the results of these tests—unless and until larger groups of elderly diabetics can be shown to have consistently impaired glucose tolerance by standards of normality such as those shown in figure 2; and, (2) the results of such tests would not influence the decision to treat these individuals with hypoglycemic agents. Thus, few, if any physicians would use hypoglycemic drugs for the treatment of elderly diabetics unless the fasting blood sugar were elevated. It is possible that better differentiation between normal and diabetic subjects at all ages might be accomplished by other procedures, such as by the use of intravenous injections of glucose in amounts larger than 25 gm., as Moorhouse et al.[12] have shown in a small group of diabetics.

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