The insulin response to glucose in patients with non-diabetic glycosuria

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Summary

Glucose tolerance tests (GTT) were performed and plasma insulin levels measured by immunoassay in eighty-nine subjects previously found to have non-diabetic glycosuria (fifty-six with renal glycosuria and thirty-three with lag curves). The time-interval between the two tests varied from 6 months to 13 years.

Ten patients had developed chemical diabetes but only three had symptoms. Two had initially renal glycosuria and eight lag curves. This significantly different incidence may have been due to an excess of older patients in the lag-curve group.

The mean insulin response was higher in those with diabetes than in those in whom the second test was normal. The individual insulin responses were abnormal by our criteria in twenty-six subjects including six of the ten diabetics. In twenty-four subjects plasma insulin levels had been measured during the initial GTT. The insulin response had been abnormal in thirteen of these, four of whom were diabetic at follow up. In contrast only one of the eleven subjects with an initially normal insulin response had developed diabetes.

It is suggested that an abnormal insulin response to glucose may be an indication of potential diabetes.

Introduction

A number of patients referred to hospital for investigation of glycosuria are found to be non-diabetic, the glycosuria being due either to a low renal threshold (renal glycosuria) or to a lag curve, in which the blood sugar rises to more than 180 mg/100 ml after glucose but returns to normal within 2 hr. The significance of such non-diabetic glycosuria is controversial. Ackerman, Fajans & Conn (1958) have reported that 63% of such patients develop diabetes but follow-up of diabetic surveys in this country (FitzGerald & Malins, 1970) has failed to

confirm this. A pointer to those at greatest risk would be of value. The addition of plasma insulin measurements (Yalow & Berson, 1960) may provide an answer if abnormalities in insulin secretion precede abnormalities in glucose tolerance. Hales *et al.* (1965) found elevated plasma insulin values in patients with mildly abnormal sugar curves but not in those with simple renal glycosuria. However, in a later series (Hales *et al.*, 1968) higher plasma insulin levels were reported in patients with renal glycosuria. In a previous study (McKiddie, 1969) an abnormal insulin response to glucose was found in twenty-three of seventy patients with non-diabetic glycosuria, and it was postulated that these twenty-three patients might be potential diabetics.

In order to study further the incidence of diabetes developing in patients originally having non-diabetic glycosuria and the insulin responses of these patients a survey was carried out of patients referred to the diabetic clinic at Glasgow Royal Infirmary between 1954 and 1967 in whom a diagnosis of non-diabetic glycosuria had been made.

Materials and methods

Of 4736 patients who attended the diabetic clinic between 1954 and 1967, 410 had well-documented non-diabetic glycosuria, 262 having renal glycosuria and 148 lag curves. Letters were sent to these patients inviting them to attend for a further test. A large proportion of these letters were returned undelivered as the catchment area of this hospital has been the site of intensive redevelopment. Replies were received from 109 patients of whom eight-nine agreed to attend for a further test, fifty-six with renal glycosuria and thirty-three with lag curves. There were sixty-five males and twenty-four females aged from 20-77 years (mean 51.8). The mean age of those with renal glycosuria (46.9 ± 15) was lower than of those with lag curves (58.8 ± 12) ($P < 0.02$). The duration of follow-up ranged from 6 months to

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13 years. There was no significant difference between the follow-up interval of the renal glycosuria group (71 ± 44 months) and the lag-curve group (58 ± 55 months).

Subjects attended after an overnight fast, having taken a normal diet for at least 3 days previously. Details were recorded of height and weight, possible diabetic symptoms, family history of diabetes and drug therapy, e.g. steroids or diuretics. Standard 50 g oral glucose tolerance tests (GTT) were performed, venous blood being removed fasting and at 30-minute intervals after the glucose load for blood sugar and plasma insulin estimation.

Blood sugar was measured as total reducing substances using a Technicon AutoAnalyzer. Plasma insulin was assayed by double antibody immuno-precipitation technique of Hales & Randle (1963) using standards and antisera as described elsewhere (Buchanan & McKiddie, 1967).

Urine was collected fasting and at hourly intervals during the GTT and tested with Clinitest tablets.

Both the first and second GTT were classified according to the following criteria:

	Blood sugar (mg/100 ml)		
	Maximum	120 min	Glycosuria
Normal	<180	<120	None
Renal glycosuria	<180	<120	Present
Lag curve	>180	<120	Present
Diabetic	>180	>120	Present

Results

The type of blood sugar curve found at the second GTT in relation to that at the first GTT is shown in Table 1. Less than half the subjects fell into the same category in the two tests, some having 'improved' and some 'deteriorated'. Ten patients (11%) had become diabetic (Table 2). Of these, eight were from the original lag-curve group whereas only two initially had renal glycosuria. This difference in incidence is statistically significant ($\chi^2 = 5.2365$, $P < 0.05$) but may in part have been due to an excess of older patients in the lag-curve group, as all diabetics were over 50 and only two were under 60 years. The blood sugar and insulin levels of these patients are shown in Table 3.

Patients with renal glycosuria at first GTT

Only two of these patients had developed diabetes. The remaining fifty-four were subdivided according to the result of the second GTT as follows: A, normal (17); B, renal glycosuria (26); C, lag curve (11). The mean blood sugar and plasma insulin levels of these three groups are shown in Table 4. Neither Group A nor B showed any significant change in mean blood sugar level between the first and second GTT but in Group C the mean blood sugar level was significantly higher in the second GTT at 30 and 60 min ($P < 0.05$, $P < 0.01$ respectively.)

Mean blood sugar levels were significantly higher at 30 and 60 min in Group B than Group A both in the initial GTT ($P < 0.05$, $P < 0.05$) and in the

TABLE 1. Comparison of results of first and second GTT

		First GTT				Second GTT			
						Normal	RG	Lag	Diabetic
Renal glycosuria (RG) 56 subjects	No	17		26		11	2		
	%	30		46		20	4		
Lag curve 33 subjects	No	5		6		14	8		
	%	15		18		43	24		

TABLE 2. Details of patients 'diabetic' at second GTT

	1st GTT	Age (years)	Sex	Symptoms	Family history	Weight at 2nd GTT (%)	Weight change from 1st GTT (lb)	Time since 1st GTT (years)
J.L.	RG	62	F	—	—	120	+ 9	6
H.D.*	RG	68	M	+	—	110	- 1	9
M.B.	Lag	69	F	+	—	102	+ 4	1½
J.H.	Lag	60	M	—	+	120	+ 9	2½
W.McD.	Lag	75	M	—	+	118	- 5	10
W.C.	Lag	76	M	+	—	98	- 2	6½
J.R.*	Lag	70	F	—	—	140	+28	2½
S.B.	Lag	50	F	—	—	140	-39	9
E.S.	Lag	58	M	—	—	120	- 1	6 months
J.McL.	Lag	66	M	—	—	98	+ 2	5 months

* On daily diuretic.

TABLE 3. Blood sugar and plasma insulin levels in the ten patients diabetic at time of second GTT

		Minutes after oral glucose													
		Blood sugar (mg/100 ml)						Plasma insulin (μ units/ml)							
		0	30	60	90	120	150	0	30	60	90	120	150		
H.D.	1	96	129	149	91	62	60	—	—	—	—	—	—		
	2	106	170	229	206	142	118	32	69	115	143	143	71		
J.L.	1	67	105	122	105	84	83	—	—	—	—	—	—		
	2	70	111	184	170	134	94	26	175	164	85	67	41		
M.B.	1	108	170	177	146	93	—	33	108	140	135	52	—		
	2	106	148	232	200	162	107	20	90	118	122	96	48		
J.H.	1	111	136	191	114	88	—	46	162	78	69	60	—		
	2	130	184	287	211	163	—	73	126	217	160	130	—		
W.McD.	1	97	210	200	160	112	77	—	—	—	—	—	—		
	2	148	340	358	262	196	—	9	35	37	30	23	—		
W.C.	1	89	191	156	100	82	82	—	—	—	—	—	—		
	2	90	208	283	177	122	107	22	183	266	75	51	31		
J.R.	1	80	165	188	124	92	—	70	158	205	136	69	—		
	2	104	252	252	282	180	—	45	226	264	118	158	—		
S.B.	1	116	171	209	166	95	—	—	—	—	—	—	—		
	2	120	152	262	250	184	147	33	68	84	67	61	51		
E.S.	1	100	180	206	140	84	76	26	72	127	140	77	40		
	2	114	188	227	179	146	112	—	—	—	—	—	—		
J.McL.	1	84	159	185	151	92	—	27	97	193	173	87	—		
	2	100	154	186	156	153	112	45	148	246	268	132	200		

TABLE 4. Mean blood sugar and plasma insulin levels of patients with renal glycosuria at original GTT subdivided according to results of second GTT

					Minutes after oral glucose											
					Blood sugar (mg/100 ml)						Plasma insulin (μ units/ml)					
					0	30	60	90	120	150	0	30	60	90	120	150
Group A Normal at 2nd GTT	Mean	39	103	1st GTT	85	116	110	92	71	70						
	S.D.	14	13		14	27	21	29	21	15						
	Mean			2nd GTT	85	117	99	87	69	68	21	116	91	56	29	21
	SD				10	20	28	29	19	11	6	50	53	34	12	4
Group B Renal glycosuria at 2nd GTT	Mean	47	105	1st GTT	90	133	126	95	77	70						
	SD	15	18		10	21	24	33	18	13						
	Mean			2nd GTT	89	141	125	94	78	76	30	172	149	81	46	35
	SD				13	25	28	29	21	18	13	84	70	51	33	16
Group C Lag curve at 2nd GTT	Mean	56	102	1st GTT	95	153	144	100	73	69						
	SD	13	19		14	19	24	24	21	22						
	Mean			2nd GTT	97	178	188	127	84	77	25	97	165	71	39	32
	SD				14	30	35	43	22	15	6	23	99	49	18	11

SD=Standard deviation.

second GTT ($P < 0.001$, $P < 0.01$). There was an even greater difference between the mean blood sugar levels of Groups A and C in the initial GTT ($P < 0.001$ at 30 and 60 min) and in the second GTT ($P < 0.01$, $P < 0.001$, $P < 0.05$ at 30, 60 and 90 min respectively). These differences might in part be due to the effect of age since glucose tolerance is known to decline with age and there was a progressive age rise from Groups A to C. However comparison of smaller samples matched for age and weight produced essentially similar results.

Comparison of plasma insulin levels during the second GTT showed similar differences, Group B having higher insulin levels than Group A at 30, 60, 120 and 150 min ($P < 0.02$, $P < 0.01$, $P < 0.05$,

$P < 0.001$) and Group C higher insulin levels than Group A at 60 and 150 min ($P < 0.05$, $P < 0.02$). These higher levels are at least in part attributable to the higher blood sugar levels.

Inspection of individual insulin responses in relation to the range of normal found in our laboratory (Table 5) showed an abnormal response in none of Group A, in 11 (42%) of Group B and in 3 (28%) of Group C. The commonest abnormality was an excessive response (12) but 2 patients had a delayed peak response.

Patients with lag curves at first GTT

The thirty-three patients were subdivided on the results of the second GTT as follows: (a) normal (5);

TABLE 5. Range of plasma insulin response found in fifty normal subjects

	Age (years)	Weight (% ideal)	Minutes after 50 g oral glucose					
			Plasma insulin (μ units/ml)					
			0	30	60	90	120	150
Range	15-65	90-110	0-50	20-240	11-175	4-124	1-68	2-51
Mean	32	101	17	81	69	32	20	19

TABLE 6. Mean blood sugar and plasma insulin levels of patients with lag curves at initial GTT subdivided according to results of second GTT

					Minutes after oral glucose												
					Blood sugar (mg/100 ml)						Plasma insulin (μ units/ml)						
					0	30	60	90	120	150	0	30	60	90	120	150	
Group (a) Normal at 2nd GTT	Mean	49	93	1st	GTT	102	186	161	121	101	89						
	SD	6	5			11	41	24	39	21	8						
	Mean			2nd	GTT	88	127	121	98	79	74	21	70	74	42	24	22
	SD					6	19	32	29	12	10	6	21	32	9	9	11
Group (b) Renal glycosuria at 2nd GTT	Mean	58	105	1st	GTT	107	185	177	113	94	89						
	SD	16	9			10	38	20	37	24	10						
	Mean			2nd	GTT	105	156	125	88	85	84	22	73	100	51	28	22
	SD					12	22	45	28	21	16	9	59	99	39	14	8
Group (c) Lag curve at 2nd GTT	Mean	59	107	1st	GTT	100	214	172	113	88	77						
	SD	14	10			16	47	56	31	16	13						
	Mean			2nd	GTT	102	215	170	103	81	76	28	126	137	72	47	38
	SD					13	46	52	41	22	13	12	65	84	58	40	24
Group (d) Diabetic at 2nd GTT	Mean	66	117	1st	GTT	100	162	189	135	90	89						
	SD	8	18			20	16	10	16	4	6						
	Mean			2nd	GTT	114	203	262	215	163	117	35	125	170	114	93	78
	SD					18	65	55	45	24	30	21	67	89	86	50	82

(b) renal glycosuria (6); (c) lag curves (14); (d) diabetic (8). The mean blood sugar and plasma insulin levels of these four sub-groups are shown in Table 6.

Both Groups (a) and (b) showed a fall in mean blood sugar level in the second test, Group (c) showed no change and Group (d) a rise in mean blood sugar levels. The mean blood sugar levels in the initial GTT were similar in all groups.

The mean plasma insulin levels were similar in Groups (a) and (b) but significantly higher in Group (c) ($P < 0.02$, $P < 0.05$ at 30 and 60 min) and in Group (d) ($P < 0.05$ at 60 and 120 min).

The individual insulin responses were judged by our criteria to be abnormal in none of Group (a), in three (50%) of Group (b), in three (21%) of Group (c) and in five (62.5%) of Group (d), the abnormalities being excessive responses in eight and low levels in three.

Patients in whom insulin levels were measured at first GTT

In twenty-four patients plasma insulin levels had been measured at the time of the initial GTT when ten had renal glycosuria and fourteen lag curves. Four of the renal glycosuria group had no demon-

strable glycosuria during the second GTT, five had persistent renal glycosuria and one a lag curve. Five of the lag-curve group had become diabetic, one had a normal curve and eight persistent lag curves.

The individual plasma insulin levels and details of these patients are shown in Tables 7 and 8. In comparison with our normal criteria the individual insulin values were abnormal in thirteen patients at the time of the original test. The excessive levels in seven of these patients may have been due partly to obesity though only three of the seven were more than 20% overweight (these three were the only subjects with elevated fasting levels). Four of the thirteen patients with an abnormal insulin response were diabetic at follow-up compared to only one of the eleven with a normal response.

During the second GTT an abnormal insulin response was found in thirteen of twenty-two subjects (in two cases insulin levels were not measured due to a technical error). In eleven subjects the insulin response was abnormal during both tests, two changed from normal to abnormal and two from abnormal to normal. In one of the latter the test was incomplete. The other patient had had numerous boils at the time of the first GTT but was completely well at the time of the second GTT.

TABLE 7. Plasma insulin levels in patients with initial renal glycosuria

Age (years)	Weight (% ideal)	Weight change (lb)	Time interval (months)	Minutes after oral glucose											
				Plasma insulin (μ units/ml)											
				1st GTT						2nd GTT					
				0	30	60	90	120	150	0	30	60	90	120	150
2nd GTT normal															
61	113	+ 6	30	10	70	46	32	16	—	36	103	194	68	21	—
19	98	- 13	8	17	64	108	89	23	20	—	152	46	42	25	24
56	116	- 8	12	24	54	82	130	160	—	29	198	170	183	149	68
45	118	- 11	9	30	57	73	205	44	—	14	194	194	37	33	18
2nd GTT renal glycosuria															
58	132	+ 2	6	70	153	273	185	98	54	65	305	245	105	45	50
62	107	- 3	8	46	192	412	343	92	72	38	132	79	—	—	—
59	115	- 6	8	21	162	205	65	54	34	17	153	196	153	37	18
49	97	+11	29	20	50	94	47	22	—	23	154	121	82	68	77
50	98	0	17	34	96	40	16	25	—	25	52	73	93	82	68
2nd GTT lag curve															
58	101	+ 5	9	21	78	175	148	26	—	31	98	288	—	38	30

TABLE 8. Plasma insulin levels in patients with initial lag curves

Age (years)	Weight (% ideal)	Weight change (lb)	Time interval (months)	Minutes after oral glucose											
				Plasma insulin (μ units/ml)											
				1st GTT						2nd GTT					
				0	30	60	90	120	150	0	30	60	90	120	150
2nd GTT normal															
63	90	- 2	12	41	81	260	223	129	137	11	42	82	49	22	13
2nd GTT lag curve															
61	98	0	12	35	104	78	48	48	—	8	99	28	14	13	10
65	114	+ 1	17	31	184	133	45	43	—	29	254	242	48	37	29
32	96	0	11	26	105	45	44	27	—	21	123	88	77	40	—
40	130	0	7	24	116	76	41	60	—	35	48	75	52	37	—
40	101	- 1	7	13	54	40	26	26	—	13	120	60	37	16	16
56	126	- 12	13	56	155	240	155	115	—	55	109	275	243	162	92
62	95	+ 4	32	12	75	82	57	32	—	32	184	118	76	43	48
59	110	- 3	8	33	136	—	122	83	44	—	—	—	—	—	—
2nd GTT diabetic															
69	101	- 4	19	33	108	140	135	52	—	20	90	118	122	96	48
66	98	+ 2	5	27	97	193	173	87	—	45	148	246	268	132	20
60	150	0	28	46	162	78	69	60	—	73	126	217	169	130	—
74	140	+28	27	70	158	205	136	69	—	45	226	264	118	158	—
56	118	- 1	6	26	72	127	140	77	40	—	—	—	—	—	—

TABLE 9. Mean blood sugar and plasma insulin levels of patients with lag curves in first GTT subdivided according to results of second GTT

	Minutes after oral glucose											
	Blood sugar (mg/100 ml)											
	1st GTT						2nd GTT					
	0	30	60	90	120	150	0	30	60	90	120	150
Group 1 (Lag 2nd GTT)	100	214	172	113	88	77	102	215	170	103	81	76
Group 2 (Diabetic 2nd GTT)	100	162	189	135	90	88	114	203	262	215	163	117
Plasma insulin (μ units/ml)												
Group 1	38	113	99	59	50	32	28	126	137	72	47	38
Group 2	40	119	149	131	69	50	35	125	170	114	93	78

Of the patients with lag curves initially the mean insulin levels of those who became diabetic were higher in the latter part of the curve than in those with persistent lag curves (Table 9) in both the first and second GTT.

Discussion

This survey has failed to confirm the high incidence of diabetes developing in non-diabetic glycosuria found by Ackerman *et al.* (1958). However the period of follow-up is relatively short and the ultimate incidence of diabetes may be much higher. It has already been shown (Hales *et al.*, 1968; Burrows, 1967; Holland, Irwin & Morgan, 1965) that subjects with renal glycosuria and/or mildly abnormal glucose tolerance may have higher insulin levels than patients with completely normal glucose tolerance. This group variation, though of considerable academic interest, is only of clinical value if it allows confident separation of those who are potentially diabetic from those who are completely normal. Burrows (1967) found that there was such wide individual variation that no clear dividing line could be found between normal and abnormal. In the present study twenty-six patients had an insulin response to glucose which lay outwith the normal range. If, as has been suggested (Ackerman *et al.*, 1958) a proportion of patients with glycosuria are destined to become diabetic, it may be those patients with an abnormal insulin response who are the potential diabetics. In keeping with this hypothesis is the finding of a greater incidence of diabetes developing in those with an abnormal insulin response. The period of follow-up is too short and the numbers too small for definite conclusions to be drawn but the evidence is certainly suggestive. It may therefore be valuable to review periodically those

individuals who have an abnormal insulin response to glucose whereas to follow-up all patients with glycosuria is time-consuming and of doubtful value.

Acknowledgment

We are pleased to acknowledge the help and encouragement given to us in this study by Dr A. H. Imrie and Professor E. M. McGirr.

We thank the Department of Biochemistry for the blood sugar estimations.

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