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Phenformin as a diagnostic tool for diabetes mellitus

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PHENFORMIN AS A DIAGNOSTIC TOOL FOR DIABETES MELLITUS

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PHENFORMIN AS A DIAGNOSTIC TOOL FOR DIABETES MELLITUS*

Phenethylbiguanide (phenformin, DBI ^{R}) has been used clinically as an oral hypoglycemic agent in the treatment of diabetes mellitus for some time; however, little information about phenformin as a diagnostic tool in diabetes has been reported. The purpose of this paper is to report on a study comparing the cortisone primed glucose tolerance test (CP-GTT) to the glucose test following oral phenformin (phenformin response test - phen-RT). It appears that phenformin does not produce hypoglycemia in normal individuals; but does produce hypoglycemia in individuals with diabetes. The reason for this difference is not fully understood (1-6).

MATERIAL AND METHODS

Selection of Subjects. Fifty adults, mostly medical students or their wives, volunteered for the study. Included were six women who had been taking oral contraceptives. The ages ranged from 20 to 33 years, with a mean age of 24.5 years. All were considered normal healthy individuals without a previous diagnosis of diabetes. Each person's history was evaluated for arteriosclerotic heart disease, (A.S.H.D.), obesity and obstetric problems known to be

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associated with diabetes. The legs were examined for the presence of pigmented pre-tibial patches, a possible precursor to clinical diabetes (7).

Experimental Design. All subjects were ambulatory during the studies but were limited in their activities. Each person had been eating a normal non-restricted diet prior to testing. A CP-GTT was completed initially, followed by a phen-RT which was performed at least one week later to avoid possible residual effects of the cortisone acetate. The CP-GTT was performed following the technique of Conn and Fajans (2), except a standard 100 gm dose of glucose was given instead of 1.75 gm/kg of ideal body weight. A blood sugar less than 160 mg percent at one hour and 140 mg percent at two hours, without the presence of glycosuria, constituted a normal response. The following technique for the performance of the phen-RT was used. Each subject fasted eight hours overnight. A venous (antecubital) blood sugar was drawn for the fasting level. Then 100 mg of phenethylbiguanide (four 25 mg DBI tablets) was administered orally. Venous blood for glucose content was drawn at the three and four hour intervals. The blood sugar was determined by the method of Somogyi-Nelson (8). (Data on all subjects presented in Appendix.)

RESULTS

Twenty-five participants had a positive family history of diabetes mellitus, and twenty-five had a negative history. Three

of the 50 cases had a positive CP-GTT with the exception of those females taking oral contraceptives. The first case (B.B.) had a one hour value of 174 mg percent and a two hour value of 143 mg percent. He had no family history of diabetes or A.S.H.D. His phen-RT was negative. The second subject with a positive CP-GTT was (A.D.) This 23-year-old female had a strong family history of diabetes, A.S.H.D. and obesity. Her phen-RT was positive. The third case was (R.R.) who had a positive CP-GTT and, subsequently, a positive standard glucose tolerance test. His family history is essentially negative except for a grandparent who died from A.S.H.D. The phen-RT in this case was positive.

The phen-RT studies on the entire group revealed an average drop of 4.76 mg percent at either the three or four hour periods with a standard deviation of 4.47 mg percent. The subjects with a positive history for diabetes demonstrated a mean decrease in venous blood sugar of 5.16 mg percent with a standard deviation of 4.68 mg percent. Those with a negative history for diabetes had a mean decrease in blood sugar of 4.21 mg percent with a standard deviation of 4.27 mg percent. Cases with a negative family history and a normal CP-GTT without glycosuria demonstrated a mean drop of 2.95 mg percent with a standard deviation of 2.95 mg percent. This group is likely to be free of diabetes.

An arbitrary value of 10 mg drop or greater was selected by us following oral ingestion of 100 mg of phenformin as an abnormal

response. This figure correlates well with the findings of Redalen et al (9) where all but five percent of subjects with a positive standard GTT had a decrease greater than 10 mg percent. Of 50 cases, nine demonstrated a drop in blood sugar of 10 mg percent or greater. Four of these subjects had a positive family history of diabetes, and five did not. The mean lowering of the blood sugar in those subjects with a positive response test was 12.5 mg percent. Only two of these cases (A.D. and R.R.) had an associated positive CP-GTT. As stated above two of three positive CP-GTT subjects had associated positive phen-RT.

Of the subjects with a positive response to the phen-RT, 78 percent had positive family histories for obesity compared to 38 percent in the entire group. Seventy-seven percent had positive family histories of A.S.H.D. compared to 54 percent for the entire group.

Because of the increasing popularity of oral contraceptives and findings of abnormal GTT's in many of these patients, it would be of interest to note the response of this group to phenformin (10). As is observed in Table I, three of six women taking oral contraceptives at the time of the study or within two months of the study had positive responses to the CP-GTT (J.S., P.A., M.N.); none of these subjects had positive responses to the phenformin test.

None of the 50 subjects was found to have the typical pigmented pretibial patches. This might well be explained by the young age of the subjects.

Table I. Results of CP-GTT and Phen-RT in Females With History of Oral Contraceptive Use.

Name	CP-GTT	Phen-RT	Use of Oral Contraceptives
D.C.	.	-	6 months
J.S.	+	-	5 months
P.A.	+	-	Quit 2 months prior
S.G.	-	-	7 months
L.H.		-	2 years
M.N.	+	-	2 years

DISCUSSION

The diagnosis of diabetes is sometimes difficult. The GTT, which still is our best test, has been shown to become positive only late in the course of the disease; yet most elderly persons test positive. Study of populations with the GTT has failed to reveal a bimodal distribution of values and thus did not clearly separate the diabetic from the non-diabetic persons. Since phenformin is known to lower the blood sugar in the diabetic and is reported to have no effect on the non-diabetic, an attempt was made to determine if phenformin could be used as a diagnostic test for diabetes. The dose of 100 mg of Phenformin-DBI ^{R} and the determination of blood sugar at three and four hour intervals were selected on the basis of the pharmacology of the drug and convenience. The study group was composed of healthy, young, ambulatory adults. About one half had a family history of diabetes. Activity during the testing procedures was kept at a minimum, although all were ambulatory. Activity of those with abnormal phen-RT seemed comparable to those with a normal test.

Of the 50 cases tested, nine manifested a decrease of blood sugar greater than 10 mg percent from the fasting level. Only four of these had a positive family history for diabetes. The absence of a positive history is not uncommon even in patients with overt diabetes. Williams reports that about one-third have a positive family history at the time of diagnosis (11). On the

other hand, a family history of A.S.H.D. and obesity was more common in the group with positive phen-RTs.

Only three of the 50 cases tested had a positive CP-GTT. Two of these had a positive phen-RT. The total number of abnormal CP-GTT is somewhat less than expected in view of the reports of Conn and Fajans who found 25 percent of the subjects with a family history of diabetes had a positive response (2). A definite point of departure in procedure was in the amount of glucose used with the CP-GTT. A standard 100 mg load was given rather than 1.75 gm/kg glucose of ideal body weight. Other factors such as the extent of family history, age and number of subjects may have been operative. In view of the fact that the CP-GTT can be normal in pre-diabetes, a positive phen-RT with a normal CP-GTT may then be a more sensitive indicator of pre-diabetes. It is emphasized, however, that the significance of a positive phen-RT in persons with a normal CP-GTT is not established. Long term follow-up studies relating to morbidity and mortality along with serum insulin and fatty acid, mycopolysaccharide, synalbumin and small vessel studies would be valuable.

The finding of a normal phen-RT in women taking oral contraceptives with an abnormal CP-GTT is interesting and needs further study.

These preliminary studies indicate that the mechanisms involved in the abnormal carbohydrate tolerance differ from those

seen in the hereditary type of diabetes and that the phen-RT may be helpful in differentiating the two.

SUMMARY

Fifty normal subjects were given a cortisone primed glucose tolerance test and a phenformin response test. Positive CP-GTT alone occurred three times; positive phen-RT alone occurred nine times; both were positive in two subjects. The significance of a positive phen-RT is not established but may prove to be a sensitive test for early recognition of diabetes. Six women included in the study were recent users of oral contraceptives. Because glucose metabolism is frequently altered in these individuals, it was interesting that three grossly abnormal CP-GTTs were found in this group whereas their phen-RTs were normal.

A new test, the phenformin response test, has been described and given to 50 normal subjects. It holds promise and should be studied further.

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APPENDIX

Results of DBI-RT and CP-GTT in Subjects With Positive History of Diabetes (Males and Females)

Name					CP-GTT (min)					DBI-RT			
Males	Ht(in)	Wt	Age	FBS	30	60	120	180	Urine	FBS	180	240	Chg
L.S.	70	190	27	84		146	86		-	77	70	73	-7
J.H.	74	180	24	88		117	86		-	82	70	68	-14
J.A.	67	145	25	88		113	70		-	72	68	74	-4
M.H.	74	180	25	86		146	114		-	81	72	72	-9
H.K.	72	162	27	76		106	103		-	72	70	70	-2
D.G.	73	250	25	81		154	101	57	-	79	68	63	-16
J.P.	72	165	28	80		105	106		-	70	64	64	-6
G.A.	73	180	23	60	102	88	72		-	49	42	50	-7
C.S.	74	195	25	56	132	151	103	46	-	77	70	76	-7
G.K.	74	215	30	74	120	103	80	72	-	74	77	77	+3
T.T.	70	240	33	66		162	100	65	-	67	63	65	-4
C.S.	68	152	25	63	165	153	92		1+	52	58	52	0
D.W.	71	184	29	60		144	84	53	1+	75	75	76	0
R.J.	73	194	25	72		120	83	80	-	70	73	72	+3
R.G.	74	160	25	81	119	137	86	72	-	44	63	71	+19
R.S.	71	145	29	71	105	114	70	60	-	82	74	81	-8
D.L.	71	170	27	77	119	88	88	63	-	59	57	53	-6
Females													
+D.C.	67	125	22	75			57		-	77	71	72	-5
+J.S.	62	113	20	112		215	200		1+	75	73	70	-5
A.D.	68	130	23	80		186	152		-	84	80	74	-10
S.S.	64	120	23	95		172	78		2+	82	71	73	-11
+P.A.	68	150	23	114		202	152		4+	76	76	71	-5
+S.G.	63	125	23	48		169	96		-	63	80	73	+10
D.R.	66	118	22	77		102	88		-	72	69		-3
#+L.H.	69	140	21	81			79		-	74	79	76	+2

+ = Taking oral contraceptives within two months of tests
# = Only a MGTT rather than CP-GTT

Results of DBI-RT and CP-GTT in Subjects With Negative History of Diabetes (Male and Female)

Name					CP-GTT (min)					DBI-RT			
Males	Ht(in)	Wt	Age	FBS	30	60	120	180	Urine	FBS	180	240	Chg
R.T.	70	170	26	62	102	76	59	56	-	64	62	63	-2
D.T.	71	170	26	90		107	99		-	76	77	76	0
K.E.	67	135	26	92		80	100		-	77	78	76	-1
G.V.	68	170	25	98		122	85		-	86	80	80	-6
W.V.	70	170	25	80		119	88		-	70	68	68	-2
W.N.	68	160	25	82		126	96		-	72	68	67	-5
R.A.	68	162	23	74		102	68	73	-	73	75	76	+2
H.G.	68	225	27	80		130	92	50	-	86	75	74	-12
R.P.	71	156	25	91		192	110		-	80	74	74	-6
C.U.	70	175	24	57	108	112	70	51	-	69	78	96	+9
D.S.	69	160	23	96		134	66	59	-	64	65	67	+1
W.T.	73	158	24	74	149	152	116	71	4+	80	68	70	-12
R.P.	73	213	26	76	167	140	94	64	-	67	54	62	-13
S.K.	70	165	24	75		153	54	67	4+	55	57	58	+2
S.S.	70	150	27	79	114	78	79	74	-	52	57	49	-3
G.B.	70	160	25	67	118	128	76	33	-	61	72	70	+9
B.B.	71	170	29	70	159	174	143	69	-	72	71	70	-2
E.M.	71	180	25	71	130	140	122		-	58	48	45	-13
L.M.	68	140	24	85		136	87		-	64	62	61	-3
R.F.	67	150	25	75		91	72		-	76	75	73	-3
D.P.	72	155	23	69	118		103	61	-	81	79	75	-6
R.N.	64	130	28	82		116	82		-	75	77	76	+1
R.R.	70	170	24	70		154	152	113	-	89	78	76	-12
D.G.	70	180	27	96		154	116		-	80	78	76	-4
Female													
+M.N.	69	140	24	99		183	149		1+	71	68	67	-4

+ = Taking oral contraceptives

Male Subjects With Positive Family History of Diabetes Mellitus

NAME	A.S.H.D. (Age)	OBESITY	OB PROBLEMS	DIABETES
L.S.	Father(48)	-	-	Brother
°J.H.	-----	-	+	Father, MGM, MGGM, PGA
J.A.	Father (46)	-	-	Mother
M.H.	-----	-	-	GM, Father, Mother
H.K.	Father (49)	-	-	Mother, MGF, PGM
°D.G.	Aunt (50)	+	-	Mother, PGF
J.P.	Uncle (49)	+	-	Uncle, MGM
G.A.	-----	-	-	GM, GM, Cousin, Cousin
C.S.	Grandmother (86) Uncle (68)	-	+	MGM, Uncle, Aunt, Aunt, Cousin
G.K.	Father (52)	+	-	Uncle
T.T.	Father (50) Grandmother (48)	+	-	GM
C.S.	-----	+	-	Uncle, Uncle, Uncle
D.W.	Father (54)	-	-	GF
R.J.	-----	-	-	Mother
R.G.	Grandfather (69) Grandmother (83)	-	-	Aunt
R.S.	-----	-	-	Uncle
D.L.	-----	-	-	MA, PU

Key: ° = Subject had 10 mg percent drop blood sugar in DBI-RT
MGM = Maternal Grandmother, etc.

Female Subjects With Positive Family History of Diabetes Mellitus

NAME	A.S.H.D.	OBESITY	OB PROBLEMS	DIABETES
D.C.	Grandfather Grandmother	+	+	Mother
J.S.	-----	+	+	Sister, GM
°A.D.	Grandfather	+	-	Father, MGF, MGGF
°S.S.	Grandmother Grandfather Great grandfather Great grandmother Aunt	+	+	GU
P.A.	-----	+	-	Aunt, Uncle Aunt, GM
S.G.	Grandfather	-	-	GGM
D.R.	Uncle Grandmother	+	-	GU, GU, GU Cousin, Uncle
L.H.	Father, Uncle, Uncle, Uncle, Uncle	-	-	PGM

°= Subject had positive DBI-RT

Subjects With Negative Family History of Diabetes Mellitus

NAME	A.S.H.D.	OBESITY	OB PROBLEMS
R.T.	Grandfather	-	-
D.T.	-----	-	-
K.E.	-----	-	-
G.V.	-----	+	+
W.V.	-----	-	-
W.N.	-----	-	-
R.A.	-----	-	-
°H.G.	Grandmother	+	-
R.P.	Father	-	-
C.U.	-----	-	-
D.S.	-----	-	-
°W.T.	Grandfather, Grandfather	-	+
°R.P.	-----	+	-
S.K.	Aunt, Aunt	+	-
S.S.	-----	-	-
G.B.	Father, Uncle	+	-
B.B.	-----	-	-
°E.M.	Grandmother, Grandmother	+	-
L.M.	Grandfather	+	-
R.F.	-----	-	-
D.P.	-----	-	-
R.N.	-----	-	-
°R.R.	Grandfather	+	-
M.N.	Aunt		

°= Subject had positive DBI-RT