Detection of Mild Diabetes Mellitus By Feeding Glucose To Induce Glycosuria

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Many physicians have recognized that mild diabetes may not be apparent if tests are made when the subjects are in the fasting state. In screening for diabetes there is, therefore, an advantage in imposing a load upon the carbohydrate metabolism to demonstrate abnormalities. During the performance of diagnostic studies on ambulatory patients, we have given 75 gm. of glucose and looked for glycosuria. When reducing substances were found in the urine, the possible presence of mild diabetes was further explored additional technics. We have attempted to evaluate , as indicators of the presence of mild diabetes, the relative helpfulness of this procedure and the frequently employed routine of securing tests of the fasting blood sugar and urine sugar.

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OUTLINE OF TECHNICAL PROCEDURES

General Plan of Study: The usual procedure was to give the experimental screening test for diabetes on the first day of study; to have tests of blood and urine before breakfast the following morning; and, in selected cases, a glucose tolerance test within the next week. The tolerance test was performed on subjects who had shown a positive screening test, particularly those who excreted a large amount of reducing substance in the urine. Exceptions to the usual procedures were made in certain cases.

Subjects: The 1000 subjects were selected from a group of ambulatory adult patients on the upper economic levels undergoing diagnostic surveys in the Private Outpatient Service of the Johns Hopkins Hospital for a variety of complaints during the period December, 1949, through November, 1951. The great majority were

white. Those selected included both sexes; save in rare instances they were over 40 years of age; in no instance had been previously recognized to suffer from diabetes; and manifested no striking symptoms of the disease. While the group did not include all patients over 40 admitted to the clinic for diagnostic study during the period in question, we can find no evidence of special selection on the basis of the clinical history or physical findings save in the case of the few subjects under the age of 40. Some in this latter group were selected for the test because of a family history of diabetes. The records of all subjects, in whom the diabetic screening test was found positive and who were subsequently evaluated by a glucose tolerance test, have been reviewed for evidence of factors other than diabetes which might cause impairment of carbohydrate metabolism; none of the group gave evidence of a recent marked restriction of caloric intake, liver disease or thyroid, adrenal or pituitary disease.

The 1000 screening tests for diabetes reported upon, represent tests on 1000 different subjects and have been selected from the first 1008 such tests performed. The 8 tests have been excluded from our report for various reasons. Three of them represented a repetition of a previous test on 3 subjects. Two of them were performed on patients previously demonstrated to have diabetes mellitus. Two of the tests were performed on patients demonstrated to suffer from pentosuria and renal glycosuria. In another test the reduction of the Benedict's solution was reported "atypical"; the patient was not further studied.

Conduct of the diabetic screening test: The test was administered to the majority of the subjects in the early afternoon. Most of them had eaten nothing since breakfast. After each subject had emptied his bladder, he drank a solution containing glucose (75 gm. dissolved in 400 ml. of water flavored with lemon juice) during the course of a few minutes. The urine collected two and one-half hours later was tested for reducing substance by Benedict's method. Subjects were instructed not to eat anything until the test was completed; no control of the intake of water was imposed before or during the test.

Technic for determination of urinary glucose: On the same day that the specimen was voided, to a test tube were added approximately 5 ml. of qualitative Benedict's solution (National Formulary) and 8 drops of urine. It is estimated that the amount of urine added varied roughly in the range 0.2 to 0.4 cc., depending on the orifice of the dropper employed. In rare instances the tube was heated over an open flame for two minutes; usually it was immersed in a boiling water bath for 5 minutes. Immediately after heating, the color of the solution was observed and the test reported as "negative", or as "positive" to various degrees—"Tr." (trace, very slight reduction giving a greenish tinge), "1+," "2+", "3+", or "4+", the final term indicating complete reduction.

Conduct of glucose tolerance tests: Tests for sugar in the urine were made by Benedict's method and all blood sugar measurements reported in our study by the Folin-Wu copper reagent[1] after tungstic acid precipitation. In the performance of the glucose tolerance test 100 gm. of glucose and 400 ml. of water were given. Venous blood was used for blood sugar determinations.

RESULTS

General: Of 1000 screening tests conducted on 1000 subjects, 809 revealed no evidence of reduction of Benedict's solution and were termed "negative" (Group O, Table 1). The urine of 191 subjects contained amounts of reducing substance varying from a trace to 4+ after the ingestion of 75 gm. of glucose. Some of these 191 subjects found it inconvenient to prolong their diagnostic study by remaining for the performance of a glucose tolerance test, and often no invitation to do so was extended by the hospital staff to those manifesting only traces of reducing substance in the urine. Hence, there was evaluated with a glucose tolerance test a relatively higher proportion of subjects manifesting heavy "glycosuria" than of subjects manifesting lesser degrees of "glycosuria." The discussion below concerns itself essentially only with those 70 subjects manifesting positive screening tests in whom the possible presence of disordered carbohydrate metabolism has been evaluated with the aid of a glucose tolerance test or, in 6 instances, the fasting blood sugar test alone. The findings on the 1000 subjects are summarized in Table 1.

Criteria for evaluating abnormal carbohydrate metabolism: We have regarded as abnormal a fasting blood sugar which exceeds 120 mg. per 100 cc. In evaluating the results of the glucose tolerance test, we have regarded as suspicious of deranged metabolism those instances in which the blood sugar level at 2 hours exceeded 119[2] and as definitely abnormal those in which the 2 hour level exceeded 139.[3, 4]

Classification of patients manifesting positive screening tests for diabetes: The subjects manifesting reducing sub-

TABLE 1 Screening Tests for Diabetes

Classification of subjects			Number subjects with indicated degree of reduction of Benedict's solution				
Designation of group	Significance of group	Total number in group	Trace	+	++	+++	++++
0	Negative screening test	809	0	0	0	0	0
1	Positive, not studied	121	50 41*	41 34	20 17	7 6	3 2
2	"False positive screening test"	21	5 24	4 19	4 24	4 19	3 14
3	Diabetes?: screening test not strategic†	18	1 5	3 17	2 11	4 22	8 45
4	Diabetes?: screening test strategic‡	31	3 10	6 19	9 29	8 26	5 16

* Underscored figures indicate proportion of group represented by figure immediately above, expressed as per cent.
† Subjects with elevated fasting blood sugar and/or glycosuria when fasting.
‡ Subjects with normal fasting blood sugar and no glycosuria when fasting. See Table 2 for glucose tolerance test.

TABLE 2 Glucose Tolerance Tests

Results on the 31 subjects in group 4, in whom the screening test was strategic to recognition of possible diabetes.

Subject	Age	Sex	Screening Test	Glucose Tolerance Test									
				Fasting		½ hour		1 hour		2 hour		3 hour	
	yrs.			Blood sugar	Urine sugar	Blood sugar	Urine sugar	Blood sugar	Urine sugar	Blood sugar	Urine sugar	Blood sugar	Urine sugar
1	63	M	2+	100	—	158	—	245	4+	164	2+	120	—
2	63	F	Tr.	96	—	168	—	215	—	200	—	120	2+
3	47	F	2+	92	—	208	—	194	—	140	—	120	—
4	58	F	1+	92	—	220	*	208	*	176	*	130	*
5	34	M	3+	100	—	190	—	234	3+	178	3+	122	Tr.
6	42	M	Tr.	100	—	178	—	214	—	214	1+	142	1+
7	63	M	1+	112	—	190	—	270	2+	200	3+	132	2+
8	40	M	4+	84	—	190	—	270	Tr.	220	4+	168	4+
9	62	M	4+	94	—	184	—	224	—	224	—	144	—
10	64	M	2+	138†	—	244	—	318	4+	238	4+	128	4+
11	43	F	3+	88	—	208	—	196	1+	158	3+	122	2+
12	56	M	4+	128†	—	200	—	244	Tr.	200	2+	124	—
13	55	M	3+	100	—	220	—	236	2+	188	2+	80	1+
14	47	M	3+	108	—	234	Tr.	255	3+	184	4+	60	Tr.
15	54	F	1+	92	—	184	—	184	—	168	—	98	—
16	56	M	3+	100	—	173	—	190	—	208	2+	84	—
17	65	M	1+	88	—	182	—	168	—	144	—	54	—
18	37	F	1+	120†	—	170	—	204	2+	152	—	60	—
19	59	M	3+	114	—	176	—	204	2+	176	3+	60	Tr.
20	55	F	3+	96	—	162	—	162	Tr.	158	—	117	—
21	53	M	2+	108	—	176	1+	159	—	152	—	84	—
22	58	M	4+	114	—	114	—	260	1+	230	4+	80	1+
23	51	M	2+	104	—	196	—	200	3+	162	4+	50	2+
24	55	F	1+	108	—	188	—	164	—	144	—	88	—
25	31	M	2+	104	—	274	1+	192	4+	148	Tr.	68	—
26	43	M	2+	100	—	208	—	152	2+	124	—	76	—
27	34	F	2+	80	—	142	—	162	—	132	—	108	—
28	53	M	Tr.	128†	—	264	—	182	2+	138	—	80	—
29	57	M	4+	94	—	164	—	182	Tr.	124	1+	54	Tr.
30	48	M	3+	104	—	159	—	164	—	128	—	68	—
31	51	M	2+	114	—	200	—	188	Tr.	128	—	56	—

* Data not available.
† Fasting blood sugar measured a few days previously was 108 mgm.% in Subject 10, 120 in Subject 12, 108 in Subject 18, and 120 in Subject 28.

stance in the urine during the screening tests have been divided into 4 groups in an attempt to determine the effectiveness of the test as an indicator of the presence of mild diabetes mellitus (Table 1).

Group 1 includes the 121 subjects who were not evaluated with a glucose tolerance test. The fasting blood sugar of 6 of these subjects was not measured. In 4 of the subjects the fasting blood sugar ranged from 124 to 132. In the remainder of the subjects the fasting blood sugar was below 121. Only 2 of the group of 121 excreted reducing substance in the fasting urine.

Group 2 includes 21 subjects, who, when subjected to a glucose tolerance test manifested a 2 hour blood sugar level below 120. These 21 patients have been characterized as manifesting "false positive" screening tests in so far as evidence of diabetes demonstrated by the glucose tolerance test is concerned. In the 16 subjects in this group in whom the routine measurement of the fasting blood sugar was made the level did not exceed 120. None of the 21 excreted sugar in the fasting urine.

Group 3 includes 18 subjects who, in addition to manifesting a positive screening test also manifested an initial fasting blood sugar in excess of 120 and, in 3 instances, reducing substance in the fasting urine. In 6 instances a tentative diagnosis at least of diabetes was established by a fasting blood sugar in excess of 139, and in 12 by the finding during a glucose tolerance test of 2 hour blood levels which exceeded this same figure. This group thus is constituted of those patients tentatively demonstrated to have diabetes in whom the possibility of the existence of the disease was initially raised by standard procedures (fasting blood sugar determination and urinalysis) as well as by the diabetes screening test.

Group 4 (Table 2) includes 31 subjects. The fasting urine was examined in 30 of the group and in no instance contained glucose. In none of the 31 was the initial fasting blood sugar in excess of 120. Subsequent to the finding of a positive screening test, all 31 patients manifested various degrees of abnormality during a glucose tolerance test. The subjects listed at the top of Table 2 are those in this group with the relatively more severe derangement of carbohydrate metabolism. Thus in Subjects 1 through 12 the blood sugar after 3 hours exceeded 119; this was not the case with Subjects 13 through 25, in whom the 2 hour blood sugar was in excess of 139, however. In Subjects 26 through 31 the 2 hour level was only slightly in excess of 119. In these 31 subjects the possible impairment of glucose metabolism was recognized only because a positive screening test led to study by a glucose tolerance test.

Significance of degree of "glycosuria" during a screening test for diabetes: Table 1 presents the frequency with which various amounts of reducing substance were found during the screening test in the 191 subjects manifesting positive tests. Several subjects with weakly positive screening tests were subsequently found to fall into categories (Groups 3 and 4) characterized by abnormal glucose tolerance tests.

Variability of presence of reducing substance in urine following ingestion of glucose: Of the 70 subjects in Groups 2, 3, and 4, (all of whom excreted reducing substance in the urine during the screening test,) 63 provided additional urine specimens for analysis during a glucose tolerance test performed a few days later. In 15 of 21 subjects in Group 2; none of 12 in Group 3; and 7 of 30 in Group 4 thus re-examined failed to excrete reducing substance detectable by Benedict's solution.

Age of subjects in each group: The average ages of the subjects in Groups 1, 2, 3, and 4 were 50, 50, 55, 50 years respectively. In each group the number of subjects whose ages exceeded the mean approximately equalled the number of those whose ages were less than the mean. There was a predominance of females in all 4 groups.

COMMENT

A strikingly high proportion (191 out of 1000) of these subjects chosen preponderantly from the middle and later decades of life, excreted reducing substance in the urine during the diabetes screening test.

Since only 70 of the 191 in question were further investigated for other evidence of possible deranged carbohydrate metabolism, no conclusion can be drawn as to the nature of the reducing substance in many instances. That the 49 subjects in Groups 3 and 4 were suspected of having at least a minimal impairment of carbohydrate metabolism, suggests a significantly high incidence of metabolic disorder in the group of 1000. The incidence would almost certainly have been demonstrated to be higher had we investigated the remaining 121 subjects with positive screening tests. (Group 1). Exactly how many of the subjects with possible impairment of carbohydrate metabolism should be characterized as suffering from diabetes mellitus is a question depending on the widely debated problem of the interpretation of a glucose tolerance test. It seems likely that, of the 18 subjects in Group 3 and the first 25 in Group 4, many suffered from true diabetes mellitus of at least a

mild degree of severity.[4] Subsequent observation of these subjects will be necessary to confirm the presence of the disease.

Whether one is justified in regarding this incidence of possible metabolic abnormality as characteristic of the general population of the United States over 40 years of age is uncertain. At least two factors were active in the selection of these patients before they applied to our hospital for care. One influence, probably tending to increase the expected incidence of discoverable metabolic abnormality, was the fact that the majority of these patients had an illness which caused them to seek medical care. Another influence, which might decrease the incidence of discoverable abnormality, was the fact that many of our patients had recently been examined by their physicians at home before coming to our hospital and no evidence of diabetes had been reported to them.

Of the total of 49 subjects with possible impairment of carbohydrate metabolism (Groups 3 and 4), in 31 (Group 4) the impairment was revealed by the finding of a positive screening test; it would have escaped detection had one relied only on the history, the fasting blood sugar and fasting urinalysis. Thus the screening test contributed significantly to the recognition of a possible metabolic abnormality in 3 per cent of the 1000 subjects in whom it was applied; it seems likely that derangement could have been demonstrated in others manifesting positive screening tests (Group 1) had they been further studied.

Of the 70 subjects manifesting positive screening tests and in whom there was additional evidence sufficient to afford an evaluation of the metabolism of carbohydrate, 21 (Group 2) were demonstrated to show a normal glucose tolerance test. Thus, 30 percent of the screening tests so evaluated were "false positives". These 21 subjects in Group 2 constituted 40 per cent of the 52 subjects in Group 2 and 4; none of the subjects in these 2 groups in whom the determinations were made manifested evaluation of the fasting blood sugar or fasting glycosuria. Since there was a tendency to pick for further evaluation with a glucose tolerance test those subjects manifesting the heavier concentrations of urinary reducing substance during the screening test, selection was in favor of studying those subjects likely to have greater derangement of carbohydrate metabolism than was present in those manifesting weakly positive screening tests. Hence it is likely that the incidence of "false positives" would be greater than 40 per cent in the 121 patients in Group 1, who were not further studied.

The known variation in renal threshold for sugar from subject to subject furnishes a likely explanation for some of the instances in which reducing substance appeared in the urine during a screening test despite the presence of ostensibly unimpaired ability to metabolize glucose, as indicated subsequently by a normal glucose tolerance test. The observation of a 2 hour blood sugar level below 120 during a tolerance test, our possibly arbitrary criterion for "normal carbohydrate metabolism", does not obviate the likely possibility that soon after the ingestion of glucose the level of blood sugar may have exceeded the renal threshold. Hence, the level of the peak of the blood sugar curve, as well as the duration of its elevation, might be expected to influence the appearance of glycosuria and hence the result of the screening test. In some instances the excretion of non-glucose reducing substances probably resulted in a positive screening test.[5]

More difficult to explain is our frequent failure to observe glycosuria during a glucose tolerance test performed subsequent to a positive screening test. This failure occurred in 22 of the 51 subjects in Groups 2 and 4 on whom data are available, or 43 per cent. It seems unlikely that this inconsistency can be completely explained by the presence of such variables as divergencies in the rate of excretion of water and variations in the proportions of urine and Benedict's solution employed during the analytical procedure. Since the screening test was often performed on the first day that the subjects visited the hospital, it seems likely that they were under greater tension at that time than during the performance of the glucose tolerance test a few days later. That emotional tension in nondiabetic subjects may be accompanied by post prandial blood sugar levels higher than those encountered during periods of greater composure has been reported by Diethelm[6]; conceivably such tension may have elevated the blood sugar in some of our subjects and therefore have contributed to the fleeting excretion of reducing substance which we sometimes observed. The glycosuria reported by some observers as an accompaniment of emotional tension in normal subjects has been tentatively ascribed by Mirsky[7] to renal influences rather than to hyperglycemia. The variability of glycosuria during the repeated conduct of a diabetic screening procedure in the same subject has been commented on by others.[8] All 12 subjects in Group 3 who were examined with a glucose tolerance test excreted reducing substance during the test; in general, the disorder of carbohydrate metabolism in Group 3 appeared more severe than that in Group 4.

To summarize our experience with the screening test, we found that in the group of 1000 subjects it was

instrumental in the recognition of possible impairment of carbohydrate metabolism in 31 who manifested no elevation of the initial fasting blood sugar and no fasting glycosuria. It was easy to supervise. The necessary analytical procedure was simple. We have not regarded the exact duration of the interval over which the urine was collected (usually two and one-half hours) as crucial; hence it has been possible for subjects to leave the laboratory area during the test for the performance of other examinations without the fear that a brief deferment of the recommended time of return to the laboratory will invalidate the results of the screening test. A definite disadvantage has been the occurrence of "false positive" results. We have no information on possible abnormalities in metabolism existing in the 809 subjects in whom the screening test was negative; despite the normal fasting blood sugar and the absence of glycosuria observed in the great majority of these 809 subjects, it seems likely that some of them suffered from mild impairment of carbohydrate metabolism which the screening test failed to demonstrate.[9]

Any screening procedure is necessarily a compromise. Factors governing evaluation of the compromise are the sensitivity and specificity of the test, its cost, and miscellaneous administrative and related factors in the environment. In the setting in which we employed it, the screening test had merit. It is our present plan to administer an abbreviated glucose tolerance test to those patients manifesting a positive screening test in which the reduction of the Benedict's solution is observed to be more than a trace; further study of patients excreting only trace amounts of reducing substance postprandially has been found unrewarding in the diabetic screening experience of others.[9] Glucose (100 gm.) will be fed and a single venous Folin-Wu blood sugar determination and urinalysis conducted 2 hours afterwards. Elevation of this blood sugar value above 119 will be regarded as evidence of possible impairment of carbohydrate metabolism and elevation above 139 as evidence of probable impairment. We shall continue to measure the fasting blood sugar at some time during the course of the diagnostic study. We would prefer to substitute for the screening test a measurement of the blood sugar 2 hours after the ingestion of glucose in all patients, if the clinic routine permitted the convenient adoption of such a screening technique. It is to be noted, however, that as with the screening test using a urinalysis, a screening procedure for diabetes involving the postprandial measurement of blood sugar has been reported to give indications of impaired carbohydrate metabolism which frequently cannot be substantiated by subsequent blood sugar determinations.[8]

Patients manifesting mild impairment of carbohydrate metabolism revealed by the screening test and subsequently confirmed by a glucose tolerance test have been told of the evidence of at least transitory impairment. Those who are obese have been instructed to lose weight. All have been advised to have examination of the blood and urine in the succeeding months and years for evidence of more pronounced impairment.

SUMMARY

An attempt has been made to discover mild diabetes mellitus by feeding glucose to induce glycosuria.

Studies were made of 1000 ambulatory patients not previously suspected of suffering from diabetes mellitus; with rare exceptions the subjects were over 40 years of age.

The urine of 191 of these patients, voided two and one half hours after the ingestion of 75 gm. of glucose, reduced Benedict's solution.

Additional studies, including glucose tolerance tests, sufficient to elucidate the possible presence of an impairment of glucose metabolism, were performed on 70 of these 191 subjects.

In 31 of these 191 subjects there were demonstrated varying degrees of impairment of carbohydrate metabolism which would not have been recognized had the studies been limited to examination of the fasting urine and measurement of the fasting blood.

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