Oral Tolbutamide Response Test In The Diagnosis Of Diabetes Mellitus

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ORAL TOLBUTAMIDE RESPONSE TEST IN THE DIAGNOSIS
OF DIABETES MELLITUS*

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There is no specific diagnostic test for mild diabetes mellitus. An apparently impaired glucose tolerance does not always signify diabetes, nor, conversely, does a normal glucose tolerance test result always signify absence of the disease. Varying degrees of impairment of carbohydrate tolerance may be seen with advancing years, obesity, starvation, pregnancy, adrenal cortical hyperfunction, thyrotoxicosis, renal insufficiency and liver disease. Normal glucose tolerance tests may be seen in mild diabetics who have been treated with diet or oral hypoglycemic agents. There is, therefore, no absolute standard against which to judge the specificity of a new diagnostic test for diabetes mellitus. However, the validity of a screening procedure may be established with reasonable certainty.

The determination of the fasting blood sugar is not an adequate screening test for diabetes, being much too insensitive. Postprandial blood sugars, while more sensitive, are difficult to interpret unless the precise content of the carbohydrate meal and the time interval between eating and blood sampling are known. Furthermore, the vagaries of gastric emptying and gastrointestinal absorption cannot clearly be evaluated.

In 1958 Unger and Madison suggested that the hypoglycemic response to intravenously administered sodium tolbutamide might be used as a test for mild diabetes mellitus. This test had the advantages of being only thirty minutes in duration, of requiring only three blood sugar determinations, and of avoiding the uncertainties in the rate of absorption of an oral glucose meal. The dangers of drug sensitivity, local reaction, and profound hypoglycemia attendant on the intravenous administration of sodium tolbutamide have been weighed against the advantages of the test and have discouraged its widespread use in the hospital or outpatient clinic.

Sodium tolbutamide is rapidly absorbed when administered orally. It is about 100 times more soluble than the ordinary tolbutamide which is used in the treatment of diabetes mellitus. Maximal blood levels of sodium tolbutamide after oral ad-

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ministration are reached in one hour, and are more than two times greater than levels achieved six hours after the oral administration of the same amount of therapeutic tolbutamide. Blood sugar values reach their nadir one hour after oral sodium tolbutamide, as opposed to four hours after oral tolbutamide. The speed of absorption of sodium tolbutamide when given orally suggested that it could be used in devising a test to separate mild diabetics from normals. In 1956 Diengott, Mirsky and Dolger\textsuperscript{4,2} had shown a marked difference in the rate of hypoglycemic response in normals from that seen in patients with mild or sulfonylurea responsive diabetes.

In 1963 Boshell, Wilensky, Wayland, and Carr\textsuperscript{4} described their results with the 30- and 40-minute oral tolbutamide response test and suggested that the 30-minute value might, when compared with the pre-test value, serve as a sensitive screening test for mild diabetes.

In this study we have attempted to determine the sensitivity of the 30-minute oral tolbutamide response test as a screening procedure to separate diabetics from nondiabetics.

\textbf{MATERIALS AND METHOD}

In this study 173 patients and volunteers were used. Their ages ranged from 18 to 86 years. While 33 subjects (19 per cent) were obese or more than 25 per cent heavier than their ideal weight, 66 patients (38 per cent) gave a family history of diabetes. This was not a normal or random population sample. Except for nine presumably normal volunteers who constituted the first subjects in the study, the patients were selected by their own physicians for carbohydrate tolerance studies on the basis of a suggestive history or physical findings. None of these patients had previously been diagnosed as having diabetes, and only three reported a history of glycosuria on some previous urinalyses.

After the determination of the fasting blood sugar, all patients were given a meal of 100 gm. of glucose in a lemon flavored carbonated beverage and a second blood sugar determination was made at the end of two hours. In addition, some patients had standard three or five-hour glucose tolerance tests, although it was felt that the two-hour blood glucose value cold adequately differentiate between patients with normal and abnormal carbohydrate tolerance. This has been demonstrated in our laboratory and recently by Keller and Hainline\textsuperscript{7} in a study of 630 consecutive glucose tolerance tests. Inpatients received diets containing 350 gm. of carbohydrate daily for three days prior to the test procedure. Outpatients received diet instructions in an attempt to insure a similar carbohydrate intake before this and the subsequent oral tolbutamide response test.
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To perform the oral tolbutamide response test (OTRT), each subject was given 2 gm. of sodium tolbutamide* in 4 tablets of 500 mg. each with 2 gm. of sodium bicarbonate in 250 cc. of water (for subjects weighing less than 55 kg., 1.5 gm. of sodium tolbutamide was used) immediately after blood had been drawn for a fasting blood sugar determination. A second blood specimen was drawn at exactly 30 minutes. In five subjects the oral tolbutamide response test was repeated after a period of diet restriction or fasting. All patients were given carbohydrate at the conclusion of the test.

Blood sugars were determined on the AutoAnalyzer using the potassium ferri-cyanide-potassium ferrocyanide oxidation-reduction method.

RESULTS

All patients whose fasting and two-hour blood sugars were less than 110 mg. per cent were considered to be nondiabetic. There were 70 patients in this group, 25 of whom (36 per cent) had positive family histories of diabetes, and 10 of whom (14 per cent) were obese. The mean blood sugar value 30 minutes after the sodium tolbutamide was 60.9 per cent of the fasting value, with a standard deviation of ±13.9 and a range from 35 per cent to 91.6 per cent.

Patients who had had two or more fasting blood sugar values over 130 mg. per cent, or whose two-hour value was 170 mg. per cent or higher were regarded as diabetics. Of 37 patients who were classified as diabetic by these criteria, 25 had fasting blood sugars of 110 mg. per cent or less, and 14 had fasting blood sugars less than 100 mg. per cent. Thirteen of these patients (35 per cent) were obese. The mean fall in their blood sugar in response to oral tolbutamide was to 84.5 per cent of the fasting values with a standard deviation of ±10. All but two of these patients (94.6 per cent) had OTRT results of 70 per cent or greater. In other words, 94.6 per cent of all diabetic patients had a fall in blood sugar to a value of 70 per cent or more of the fasting value.

There were 65 patients whose two hour blood sugar values were greater than 110 mg. per cent and less than 170 mg. per cent. The mean fall in the fasting blood sugar in response to oral sodium tolbutamide in this group was to 63.1 per cent of the fasting value, a figure not significantly different from that obtained in the clearly nondiabetic group. The standard deviation was ±14 and the range was from 32 per cent to 92 per cent. These values were essentially the same as those obtained in the presumably nondiabetic group.

*Sodium tolbutamide tablets were generously supplied by Dr. Thomas J. Vecchio, The Upjohn Company, Kalamazoo, Michigan.
ORAL TOLBUTAMIDE RESPONSE TEST
COMPARSED WITH FASTING BLOOD SUGAR

Frequency distribution of OTRT values at each fasting blood sugar level. Patients in each group are further divided into those with negative and positive family histories of diabetes mellitus.

The results of the OTRT were then compared with the fasting blood sugar values and were found to correlate positively at each level, showing a more marked rise in that group with fasting blood sugars over 110 mg. per cent. (Figure 1) In each instance the mean values for those patients with positive family histories of diabetes were slightly higher than those with negative family histories, suggesting that there may have been more diabetic patients in those groups with positive family histories.

When compared with blood sugars two hours after 100 gm. of glucose there was no correlation until two-hour values exceeded 140 mg. per cent, at which level
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Frequency distribution of OTRT values at each level of blood sugars obtained two hours after 100 gm. of glucose given orally.

the mean OTRT rose from about 60 per cent of the fasting value to 78 per cent of the fasting value. (Figure 2)

In comparing the results from the diabetic and nondiabetic group, it was noted that 35 of the 37 diabetic patients, or 95 per cent, showed 30 minute specimens above 70 per cent of the pre-test value.

Among the nondiabetics, 96 per cent showed 30-minute sugars which were below 85 per cent of the fasting value. Of these nondiabetic patients 69 per cent had values below 70 per cent of the pre-test value. Of the 22 presumably nondiabetic patients showing results above this value (31 per cent), over half (55 per cent) were obese or had a positive family history of diabetes or had specific symptoms or signs frequently associated with diabetes such as necrotizing papillitis, recurrent pyelonephritis, recurrent
Frequency distribution of OTRT values in diabetic and nondiabetic subjects. The middle column represents patients from the nondiabetic group who had positive family histories of diabetes or who were obese or had symptoms suggesting diabetes mellitus.

Examining the nondiagnostic range of OTRT values falling between 70 per cent and 85 per cent of the pre-test blood sugar, we noted that this area included 58 patients or about 33 per cent of the patients tested. When judged by the fasting and two-hour blood sugar levels after 100 gm. of glucose, 65 patients or 38 per cent were in an equivocal or nondiagnostic area.

In the nondiagnostic zone of the OTRT, 18 patients (31 per cent) were subsequently shown to be diabetic, 19 (33 per cent) patients were probably nondiabetic...
Graph showing the distribution of response to oral sodium tolbutamide in 173 subjects. The division into diabetic, equivocal, and nondiabetic is based on the fasting and two-hour blood sugar values after 100 gm. of glucose. Of diabetic patients 95 per cent showed a 30-minute fall in their blood sugar to a level greater than 70 per cent of the pre-test value (indicated by the vertical line). Of the normals 96 per cent showed values below 85 per cent.

and 21 patients (36 per cent) were in an equivocal zone by either test procedure. (Figure 4)

There were no reactions due to drug toxicity. Hypoglycemic symptoms occurred during the test in only a few nondiabetic subjects but these were mild and in no instance was it necessary on this account to terminate the procedure before the 30-minute period. The lowest blood sugar recorded was 27 mg. per cent and this occurred in only one patient. In the group of nondiabetic patients, 8 per cent showed blood sugars below 40 mg. per cent at 30 minutes. Some diabetic patients reported hunger or nervousness occurring later in the day but in no instance was this particularly distressing. There was no syncope or confusion in any instance.
In 1958 Unger and Madison report their results with the intravenous tolbutamide response test in 79 mild diabetics and 100 nondiabetics. The criteria which they used for distinguishing diabetics from nondiabetics on the basis of carbohydrate tolerance were similar to those used in this study. Their results led these investigators to set up the following diagnostic criteria:

1. In nondiabetics the 20-minute blood sugar dropped to less than 75 per cent of the pre-test value.
2. The range of 75-84 per cent was felt to be nondiagnostic.
3. The range of 85-89 per cent signified probable diabetes.
4. If the 20-minute blood sugar value was 89 per cent of the fasting sugar or higher, the patient had diabetes.

Furthermore, Unger and Madison report a mean 20-minute value in their nondiabetic group as 60 per cent (SD ±13.9). This seemed to confirm the observation of Boshell, et al. that the response to orally administered sodium tolbutamide lagged about 10 minutes behind that following the intravenous route. Whitehouse and Lowrie suggested that a blood sugar of 80 per cent of the pre-test value 30 minutes following intravenous sodium tolbutamide separated diabetics from nondiabetics.

In the 33 diabetic patients in this study, the mean blood glucose concentration at 30 minutes was 84.5 per cent of the fasting value (SD ±10), compared with Unger and Madison's reported mean value of 90 per cent (SD ±7.4) in 79 mild diabetics.

From our data we believe we can suggest the following interpretation of test results for the oral tolbutamide response test:

1. Thirty-minute blood sugar values which are 70 per cent or less than the pre-test value probably signify absence of diabetes.
2. The range of 70 per cent to 84 per cent is nondiagnostic.
3. The range of 85 per cent to 94 per cent signifies probable diabetes.
4. All patients with 30-minute values of 95 per cent or higher are diabetic.

Boshell and co-workers in their study of the OTRT report similar results, although it should be pointed out that their study, like that of Unger and Madison included distinct population groups of diabetics and nondiabetics. In neither study were patients included who showed equivocal or nondiagnostic results on carbohydrate tolerance tests.

The inclusion of this group in our study complicates the results, especially since that group which showed equivocal results by the carbohydrate tolerance tests was
not the same as the group showing equivocal or nondiagnostic results by the oral tolbutamide response test. To be sure, the two groups did overlap. There were 65 patients who were in the questionable range of carbohydrate tolerance, and 58 in the nondiagnostic range of sodium tolbutamide response. Twenty-five patients appear in both groups (Figure 4). This would suggest that both tests may be of approximately equal value as screening procedures. A more important observation may be, however, that the two tests are measuring related but separate phenomena. What clinical significance this may have must, of course, depend on subsequent observation of the clinical courses of the patients in the two groups.

There is some suggestion that patients with diseases other than diabetes, such as hepatic cirrhosis or thyrotoxicosis, which interfere with a normal response to a carbohydrate load, may show a normal response to oral sodium tolbutamide but impaired carbohydrate tolerance. This was true in two patients with cirrhosis who had OTRT values less than 70 per cent but two-hour blood sugars over 200 mg. per cent. One patient with thyrotoxicosis had an OTRT result of 75 per cent, and a two-hour blood sugar over 250 mg. per cent.

Variation in the rate of absorption of a monosaccharide such as glucose may markedly reduce the reliability and even the reproducibility of the oral glucose tolerance test. Monosaccharides are absorbed into the blood almost entirely in the small intestine, with only small amounts absorbed directly from the stomach. A delay in gastric emptying could result in an abnormally high two hour blood sugar value and consequently, if it occurred with sufficient frequency, in the overdiagnosis of diabetes mellitus. That this in fact may occur has been suggested by the rather high prevalence of abnormal glucose tolerance curves in both random and selected population samples. Conversely, slow or delayed absorption may yield a nondiagnostic “flat” glucose tolerance curve.

The frequent lack of reproducibility of glucose tolerance values suggests that these factors of glucose absorption and gastric emptying vary from time to time in the same individual. The rapid absorption of sodium tolbutamide across the gastric mucosa makes this test more reliable and reproducible. In this study we do not have sufficient numbers of repeated tests to support or refute this hypothesis. In three obese patients the test was repeated after 7-10 days of fasting. In each instance there was a diminished response to sodium tolbutamide (78-85 per cent; 72-87 per cent; 78-86 per cent). This was a predictable result.

When the test was repeated without a change in dietary preparation in two patients the results varied by less than 3 per cent.

In comparing fasting blood sugars with the results of the OTRT we see that 82 out of 83 patients who had OTRT results of less than 70 per cent had fasting blood sugars at or below 110 mg. per cent.

In the nondiagnostic range of 70-84 per cent there were 58 patients, 15 of whom had blood sugars of 110 mg. per cent or higher.
In the range of probable diabetes with OTRT results of 85 per cent or higher there were 24 patients, 12 of whom had normal fasting blood sugars.

In a series of over 1000 glucose tolerance tests reported by Hainline and Keller,\textsuperscript{11} 53 per cent of those patients with fasting blood sugars of 110 mg. per cent or less had abnormal or equivocal glucose tolerance test results.

In our study 156 patients had fasting blood sugar values of 110 mg. per cent or less. Of these patients, 32 per cent had abnormal or equivocal results from the OTRT. This suggests that the OTRT is more sensitive than the fasting blood sugar as a screening test for diabetes mellitus but either less sensitive\textsuperscript{12} or more specific than the oral glucose tolerance test.

**Conclusions**

The response of the blood sugar to oral sodium tolbutamide at 30 minutes may be used as a sensitive screening test for diabetes mellitus. Of the mild diabetic patients in this study, 95 per cent had blood sugars 70 per cent or higher than the pre-test value 30 minutes after the ingestion of sodium tolbutamide. All patients whose blood sugars dropped to a level of 95 per cent or more of the pre-test value at 30 minutes were diabetic, and in this range the test proved to be diagnostically specific.

Equivalent or nondiagnostic results appear with both this test and the abbreviated two-hour glucose tolerance test in about one third of all subjects tested.

The oral tolbutamide response test is simpler and apparently safer than the corresponding intravenous test. It seems to yield correspondingly sensitive results, although perhaps somewhat less specific.

**Summary**

The 30-minute oral sodium tolbutamide response test was evaluated in 173 patients by comparing it with the results of fasting blood sugar and blood sugar two hours after the ingestion of 100 gm. of glucose.

There were 37 mild diabetic patients in this group and 70 nondiabetics. The remaining 66 patients had two-hour blood sugars falling in the equivocal range (110-170 mg. per cent).

The mean value for the blood sugar 30 minutes following 2 gm. of oral sodium tolbutamide (1.5 gm. in patients weighing less than 55 kg.) administered with 2 gm. of sodium bicarbonate, was 60.9 per cent of the pre-test value (SD ±13.9) in the nondiabetic, and 84.5 per cent of the pre-test value (SD ±10) in the diabetic group.

Of the diabetic patients 95 per cent had a fall in blood sugar to 70 per cent or more of the pre-test value.

Of the nondiabetic patients 96 per cent had 30-minute values less than 85 per cent of the pre-test value.
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Of the patients whose test results fell between these figures, about one third were subsequently shown to be diabetic.

All patients whose 30-minute blood sugars were 95 per cent or greater than the pre-test value were diabetic.

The 30-minute oral tolbutamide response test qualifies as a sensitive screening test in the diagnosis of diabetes mellitus.

The significance of the lack of correlation between the equivocal or nondiagnostic values of the oral tolbutamide response test and the abbreviated oral glucose tolerance test will perhaps become clear with prolonged observation and retesting of patients in these groups.

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