Glucose Tolerance Test Standardization Simplified by Urinary Ketone Testing

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AN AVERAGE 3-day intake of 300 grams of carbohydrate is commonly recommended prior to the oral glucose tolerance test (*1*) in order to avoid misdiagnosis due to "starvation" diabetes. Recent studies question the need for such rigorous standardization, since lesser intakes have proved adequate (*2–5*). Alternative plans have not received universal acceptance (*6*), however, for the exact level at which the prior carbohydrate intake affects the results of the glucose tolerance test remains unknown. Our aim is to examine the relationship of ketonuria to low carbohydrate intake and altered blood sugar levels, with possible simplification of glucose tolerance test standardization as our major objective.

Starvation or carbohydrate privation is associated with increased fat mobilization and utilization, as reflected by elevated levels of plasma-free fatty acids and ketones (*7–9*). The consequent ketonuria (*7*) is readily accessible for simple and objective testing. Such a test, being a guide to metabolic alterations during starvation, should prove more valuable than sole reliance on dietary prescriptions or estimated food intakes.

Material and Methods

Serial tests performed on persons under observation primarily for other purposes formed the basis of this study (*10*). Two separate groups of sequential tests were examined. Glucose tolerance tests given to pregnant women (group A) whose prior carbohydrate intake averaged less than 150 grams daily were compared with tests performed on the same women in a preceding or succeeding pregnancy when carbohydrate consumption had been adequate. Results of annual tests on nonpregnant women (group B) whose previous carbohydrate intake had fallen below 150 grams were compared with tests when this limit had been met or exceeded by the same subjects.

For both groups, routine preparation for the glucose tolerance test consisted of (*a*) recommending a daily food intake in excess of that eaten at usual meals and calculated to give a minimum 3-day average of 250 grams carbohydrate, (*b*) requesting that a food intake diary be kept during this 3-day period, and (*c*) having a nutritionist assess the actual level of carbohydrate consumption during this period by reviewing the patient's food diary and dietary history on the morning of the test.

Supplementary data were obtained from files kept on persons participating in two previously published studies (group C), consisting of the administration of diets of known carbohydrate content to institutionalized patients following glucose tolerance tests (*2*, *3*). Records indicating that a patient's urine had been tested for acetone on the morning of a glucose tolerance test were submitted to further analysis.

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All glucose tolerance tests were performed following an overnight fast. Glucose was administered as a 50 percent solution containing 100 grams. Specimens of venous blood were drawn into fluoride tubes for analysis by the Somogyi-Nelson method or by the comparable Hoffman ferricyanide method on the Auto Analyzer (*11*). Urine specimens of group B and group C patients were tested shortly after collection, using Acetest tablets (*A*). In rating persons with a positive acetone, trace reactions were considered negative.

Results

Group A. Blood sugars obtained after fasting and 1 hour following 100 grams of glucose administered orally to 180 pregnant women are shown in table 1. Results indicate that there is no significant difference ($P>.05$) between the mean blood sugars whether or not they had been preceded by an average 3-day carbohydrate intake of less than 100 grams or 100 to 149 grams and 150 grams or more in further tests on the same individuals. These comparative tests were obtained from the woman's preceding or subsequent pregnancy. The median age and weeks' gestation at which the test was performed were similar on each occasion. Examining the same results by the differences between the low-intake and higher-intake tests for each woman, rather than the mean for the group, confirms that no change in blood sugars exists for the carbohydrate intake levels under examination (table 1).

Group B. Results of two tests with differing prior food intake on each of 167 nonpregnant women are given in table 2. Again there is no statistically significant difference ($P>.05$) between the mean blood sugar level when tests in those with intakes below 100 grams or 100 to 149 grams are contrasted with other tests performed on the same persons but preceded by an intake in excess of 150 grams. Similarly, there was no variation in the average age at the time these comparative tests were administered. Further confirmation of the blood sugar findings is found when differences between the two tests are subjected to a more searching individual examination (table 2). Urinary ketones were obtained on the women in this group whose prior intake averaged less than 100 grams. It is of particular note that all such tests were negative.

Group C. The figures in table 3 are taken from previous studies (*2,3*) on the basis of

Table 1. Mean blood sugar levels of 180 pregnant women (group A) with low and adequate carbohydrate intakes

Previous 3-day carbohydrate intake (grams)	Number of women	Blood sugar (mg./100 ml.)		
		Fasting	1 hour post 100 grams glucose	
Less than 100 (low)	23	69. 2 ± 9. 5	97. 5 ± 29. 0	1-hour difference by individuals −2.1 ± 5.8 S.E.
150 or more (adequate)	23	68. 3 ± 9. 5	99. 6 ± 28. 2	
100 to 149 (low)	157	71. 9 ± 11. 1	113. 7 ± 33. 1	1-hour difference by individuals 2.2 ± 2.2 S.E.
150 or more (adequate)	157	71. 7 ± 10. 6	111. 5 ± 29. 0	

Table 2. Mean blood sugar levels in 167 nonpregnant women (group B) with both low and adequate carbohydrate intakes

Previous 3-day carbohydrate intake (grams)	Number of women	Blood sugar (mg./100 ml.)		
		Fasting	1 hour post 100 grams glucose	
Less than 100 (low)	36	80. 5 ± 13. 5	121. 9 ± 32. 3	1-hour difference by individuals 3.6 ± 4.7 S.E.
150 or more (adequate)	36	82. 6 ± 10. 4	118. 3 ± 42. 9	
100 to 149 (low)	131	81. 5 ± 11. 5	113. 2 ± 37. 1	1-hour difference by individuals 2.1 ± 3.1 S.E.
150 or more (adequate)	131	81. 7 ± 10. 7	111. 1 ± 35. 0	

availability of urine ketone information. Glucose tolerance tests, performed when a previous carbohydrate intake of less than 100 grams had been taken, varied significantly from tests on the same 46 persons following a normal intake. The difference consisted of a lower fasting and higher 1 hour post-glucose value following the inadequate intake. Analysis of these findings by the urinary ketone results are also shown in table 3.

In the low-intake group those with ketonuria had the highest blood sugar values after receiving glucose, whereas those without ketonuria did not differ significantly from the entire group on a high intake. Thus the impression of diminished tolerance in the low-intake group as a whole may be attributed to the altered response to glucose of the persons with ketonuria. Persons with a trace reaction for ketone bodies were considered negative because of the possible errors in judging this minimal color change with a clinical semiquantitative test and because their blood sugars were not different from those with negative tests. To examine the practicability of using ketonuria for routine application, the data in the figure were compiled. The rise in mean blood sugar level paralleled the increased frequency of ketonuria. Persons with positive urinary ketones do not necessarily have a positive glucose tolerance test by specific criteria (*6*, *12*). On the other hand, the eight persons positive to one or other of the tests all had ketonuria.

Mean blood sugar values on group C persons with a prior intake of 50 grams or less showed no significant separation of the post-glucose value when examined by less than 3 pounds and more than 5 pounds weight-loss groups. That weight loss is related to the problem, however, is indicated by the significantly greater weight decrease (mean difference 1.6 pounds) in persons with ketonuria in contrast to those without ketonuria.

Discussion

Instructing patients as to the necessity and means of attaining high carbohydrate intakes prior to glucose tolerance tests is relatively simple though time consuming. Evaluation of the intake on the patients' return 3 or more days later is, however, subject to many errors. Problems with history items have been well documented, notably in circumstances subject to blind confirmation (*13*) or later verification (*14*). The use of dietary diaries helps to circumvent some of these problems. This device, however, depends on the full cooperation of the subject as well as the presence of persistence and a realistic attitude. Even under ideal circumstances such data must necessarily be considered in the realm of hearsay evidence. Reliance on an administered diet or the calculated intake as a basis for judging the adequacy of preparation for the oral glucose tolerance test, therefore, has obvious drawbacks.

Body weight, size, habits, and metabolic needs vary greatly. Consequently, to expect that one level of carbohydrate intake should be suitable for all persons seems unreasonable. Our data reflect this by the variation in weight reduction in persons deprived to the same degree of carbohydrates. It is also manifested by the fact that not all persons have altered blood sugar levels

Table 3. Glucose tolerance and ketonuria in 46 persons (group C) with low and adequate carbohydrate intakes

Carbohydrate intake	Ketonuria	Number of persons	GTT code letter	Mean glucose tolerance test, blood sugar (mg./100 ml.) Fasting	1 hour	2 hours	3 hours
100 grams	Positive	32	(A) [1]	67.1±11.6	149.8±40.1	119.8±38.1	83.4±31.5
Less than 100 grams.	Negative	14	(B)	77.5± 6.7	114.9±29.6	86.7±22.9	72.1±18.0
Total		46	(C) [2]	70.3±11.4	139.2±40.3	109.7±37.1	79.9±28.3
Mean 285 grams	All negative	46	(D)	81.2± 9.5	99.9±32.9	84.4±28.1	65.4±21.8

[1] All GTT values significantly different ($P < .05$) from mean GTT (B) and (D) except the third-hour value of GTT (B).
[2] All GTT values significantly different ($P < .05$) from mean GTT (D).

Percentage of persons with ketonuria at various levels of carbohydrate intake with mean 1-hour, post-glucose blood sugars

Previous carbohydrate intake (grams)	Number of persons	Mean one hour blood sugar (mg./100 ml.)	Percent with ketonuria
20	18	159.1	94.4
50	19	133.3	68.4
100	9	111.8	11.1
150	18	116.2	0.0
100 and less	46	139.2	67.3
Greater than 150	46	99.9	0.0

following marked dietary restrictions. Finally, it can be inferred from the variations in urinary acetone excretion in persons taking the same low carbohydrate diet. From this viewpoint, an alternative method of gauging the effect of carbohydrate privation in relation to the person's needs seems desirable.

Results of our studies confirm that mean post-glucose blood sugar levels rise with carbohydrate restriction. The more severe the restriction the greater the certainty that a person will show this increase. Such restrictions are associated with a weight loss, but the relationship of the degree of this weight loss to rise in blood sugar levels cannot be applied with any confidence to the person, as indicated by weight changes within 1 week of the test. Ketonuria, on the other hand, is related more closely to the degree of carbohydrate restriction. It occurred in 17 of 18 persons on a 20-gram carbohydrate diet, 13 of 19 on a 50-gram diet, and 1 of 9 on a 100-gram diet as shown in the figure. Just as blood sugar results on such low diets do not necessarily become elevated in every case, so persons with positive ketonuria do not necessarily have high blood sugars. As a group, however, the blood sugar rise associated with carbohydrate restriction was found to result from the increase seen in persons exhibiting ketonuria. Confirming the value of ketonuria in this respect is the fact that all persons initially normal but becoming positive to the oral glucose tolerance test, using widely accepted criteria, had ketonuria. None of the low-intake group with negative ketones met these diagnostic levels.

An average carbohydrate intake of 100 grams or less for 3 days had a significant effect on blood sugar levels in group C but not in group A or group B patients. One obvious explanation between these differing sets of results is that the group C data were obtained from persons in institutions where the prior carbohydrate intake could be supervised, while the group A and group B data were obtained under routine clinical outpatient conditions. Furthermore, the majority of the institutionalized patients had, in fact, intakes of 50 grams and lower while the pregnant and nonpregnant groups, with one exception, had intakes above 50 grams. Finally, where group B patients showed no significant rise in blood sugars when their previous carbohydrate intake fell below 100 grams, all had a negative test for urinary ketones on the morning of the glucose tolerance test.

Routine testing for ketonuria should give confidence in the adequacy of a person's metabolic status to insure standard conditions for judging glucose tolerance. The test is simple and rapid and has the additional merit of being an objective measure. Increased confidence resulting from this objective test leads to additional advantages in that the time and skills of a physician or trained nutritionist may also be conserved.

Summary

A rise in post-glucose blood sugar levels following carbohydrate privation, while occurring primarily in persons with an intake below 100 grams, resulted from the diminished tolerance in those persons having ketonuria on the morning of the glucose tolerance test. A fall in fasting blood sugar values with carbohydrate restriction also occurred in those persons with ketonuria.

Reliance on dietary prescriptions or intake estimations to insure the adequacy of prior carbohydrate intake for purposes of avoiding misdiagnosis due to so-called "starvation" diabetes is questioned. Simple semiquantitative testing for urinary ketones is recommended as an alternative. It has the advantage of being objective and takes into consideration varied individual requirements due to differing metabolic needs.

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EQUIPMENT REFERENCE

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