Nausea and vomiting have been recurrent problems with the oral glucose tolerance tests (OGTT) used to diagnose diabetes. We believe the nausea is associated with delayed gastric emptying caused by the high osmolality of the glucose solution. In our pilot study, both the “standard” 100-g glucose OGTT and our new modified (lower osmolar) glucose solution were evaluated. Considerably delayed gastric emptying (along with severe nausea) was consistently noted with the standard OGTT. No nausea and a much more rapid gastric emptying time were recorded when the modified glucose solution was administered. We were able to diagnose diabetes (by using Wilkerson’s point system) when our modified OGTT was administered to type 2 diabetics. We plan to develop a more physiological, more reproducible, and better tolerated OGTT to diagnose diabetes more accurately in the general population.

Additional Keyphrase: diagnosis of diabetes

Glucose loading tests for the diagnosis of diabetes mellitus were first introduced by Jarney and Isaacsen in 1918 (1). Although wide variations in results due to age and obesity (2) were reported in the 1920s, John’s report of his results of 1100 oral glucose tolerance tests (OGTTs) in 1929 (3) led to the widespread use of the test to detect those with undiagnosed diabetes. Only in the last 20 years has the limited value of OGTT as a diagnostic procedure, when applied to the general population, become obvious. Soaskin (4), Danowski et al. (5), and Andres (6) had suggested that the diagnosis of diabetes was being made erroneously (false-positive diagnosis) in many individuals because the criteria used for interpretation were inappropriate. Others have proposed various schemes for administration and interpretation of the OGTT (7–9). The different protocols for OGTTs differ in the amount of glucose administered to the patient, the time at which blood is drawn, and the interpretation of the numerical results. Both the large intraperson and interperson variations during an OGTT have been emphasized (10, 11). With all of the different variables and disagreements as to interpretation, the OGTT, the most popular test for the diagnosis of diabetes or “impaired glucose tolerance,” continues to be considered controversial.

However, no one has taken into consideration the osmolarity of the oral glucose solution and the difficulty in gastric emptying caused by its hyperosmolarity. We believe this delayed gastric emptying not only is responsible for the difficulty in interpretation of the OGTT but also for the nausea and vomiting experienced by most patients who undergo an OGTT. Our pilot study examined the effects on gastric emptying of the standard 100 g of glucose (1.85 mol/L) compared with a new modified 50-g (0.62 mol/L) glucose solution. We also evaluated (a) the reliability with which our new modified OGTT can be used to diagnose diabetes mellitus; and (b) patients’ symptoms (nausea and vomiting) with both the “standard” and our modified OGTT.

Materials and Methods

Subjects. We evaluated 13 volunteers, using our new modified OGTT. All patients were between 27 and 42 years old and all had been fasting for longer than 10 h before each test. Four patients were known (type 2) diabetics. Standard OGTTs were also administered to a diabetic and a nondiabetic volunteer.

Glucose beverage. We used “Glucose Tolerance Test Beverage,” lemon–lime flavor (General Scientific, Richmond,
VA 23228) for both the standard and modified OGTT. For the standard test, 100 g of glucose (1.85 mol/L), the contents of the entire bottle, was ingested within 5 min. For the modified OGTT, 50 g of glucose (half the bottle’s contents) mixed with 450 mL of water (final concentration 0.62 mol/L) was ingested within 5 min.

Gastric emptying. We performed gastric-emptying studies with a gamma camera (Scintronix USA Inc., Woburn, MA 01801), using both the modified and routine OGTTs, on a diabetic volunteer and a nondiabetic volunteer. These studies were performed at least one week apart to prevent any residual radioactive material from interfering with interpretation of the nuclear scan. About 200 µCi of 99m technetium sulfur colloid (99m Tc-SC; CIS-US, Bedford, MA 01730) was added and stirred into each glucose solution. The 99m Tc-SC was labeled at a local radiopharmacy (Diagnostic Medicine Inc., San Antonio, TX 78229). The volunteers drank all the glucose solution within 5 min shortly after the 99m Tc-SC was added to the solution.

The volunteers were then placed in a semi-reclining position (45° from horizontal) and the gamma camera was positioned anteriorly. Data were collected continuously and summed at 30-s intervals. Images were acquired until at least half of the glucose solution had emptied from their stomachs.

The Scintronix gamma camera was used with a low-energy, all-purpose collimator at a 20% window setting centered at 140 keV. It was connected to a computer (Medical Data Systems, Ann Arbor, MI 48108). A region of interest corresponding to the stomach was selected. Counts in this region were calculated in each 30-s image. After correcting for radioactive decay, the count rate of the region of interest was converted to percentage of the maximum count rate recorded.

Serum samples. Peripheral venous blood was sampled for determination of serum glucose before the beginning of the OGTT (0 min), then 30, 60, 90, and 120 min later. The blood was collected in grey-top (potassium oxalate and sodium fluoride) Vacutainer Tubes (Becton Dickinson Vacutainer Systems, Rutherford, NJ 07070).

Glucose assay. Serum glucose was measured with the "Paramax" instrument (Baxter Healthcare Corp., Irvine, CA 92718–2017) by a modification of the coupled enzymatic method of Stein (12). The modifications involve the use of NAD⁺ rather than NADP⁺ and glucose-6-phosphate dehydrogenase (G-6-PDH) from Leuconostoc mesenteroides rather than yeast. Glucose is phosphorylated to glucose 6-phosphate in the presence of hexokinase, converted to 6-phosphogluconate in the presence of G-6-PDH, and NAD⁺ is reduced to NADH, causing a change in absorbance, which is monitored bichromatically at 340/405 nm. The assay temperature is 37 °C.

Study Protocol

Gastric-emptying study. After a 10-h fast, one nondiabetic volunteer and one type 2 diabetic were initially given the standard 100 g of glucose in 300 mL of water (one bottle of Glucose Tolerance Test Beverage) to which had been added 200 µCi of 99m Tc-SC. A gastric emptying study with sequential imaging was then performed, with blood being drawn simultaneously according to the standard OGTT protocol.

One week later our modified OGTT was administered to the same two volunteers while the gastric emptying study was being performed.

Modified glucose tolerance test. Four known type 2 diabetics and nine nondiabetic volunteers were given our modified OGTT in the early morning, after a 10-h fast. Blood was drawn from the seated volunteers at 0, 30, 60, 90, and 120 min after they ingested the glucose solution.

Results

Gastric emptying was inhibited in the standard OGTT as compared with the modified OGTT, as seen in Figures 1a, b, and c. Although gastric emptying was faster for the diabetic volunteer, both the nondiabetic and the diabetic subjects had 50% or more of the standard oral glucose solution in their stomach an hour after the solution was ingested. Much more rapid gastric emptying was observed with the modified solution, allowing glucose to enter the peripheral circulation faster. The half-emptying time was approximately twice as long with the standard OGTT (105 min) as with the modified OGTT (52 min) in the non diabetic volunteer.

Utilizing data on half-emptying time from the gastric emptying studies, we calculated that 1.90 kcal were delivered per minute to the duodenum with the standard OGTT, whereas 1.92 kcal were delivered per minute with the modified OGTT; a volume of 1.5 mL was emptied from the stomach per minute in the standard OGTT, 4.5 mL/min with the modified OGTT. The volunteers experienced moderate to severe nausea each time the standard OGTT was administered as compared with no nausea on any of the 13 times the modified OGTT was administered.

Results of a survey of 10 hospitals in our area revealed that the OGTT is administered by the hospital phlebotomist or laboratory personnel. After blood and urine sam-

![Fig. 1. Gastric emptying studies showing: (a) residual labeled glucose remaining in the stomach after 70 min with a standard 100 g OGTT; (b) after 70 min with modified OGTT; (c) residual labeled glucose remaining in stomach after 120 min with standard OGTT; (d) after 120 min with modified OGTT](image-url)
Fig. 2. Gastric emptying in a nondiabetic volunteer, showing more rapid gastric emptying of the modified oral glucose solution

Fig. 3. Gastric emptying in a type 2 diabetic volunteer, showing more rapid gastric emptying of the modified oral glucose solution

Fig. 4. Results of the modified oral glucose tolerance test administered to nine nondiabetic volunteers. The serum glucose clearly peaks at 30 min.

Fig. 5. Results of the modified oral glucose tolerance test administered to four type 2 diabetic volunteers. The serum glucose clearly peaks at 1 h or later.

Discussion

In its early stages, diabetes mellitus is still extremely difficult to diagnose. Although good methods are now available for measuring plasma insulin (14) and for the quantification of diabetic microangiopathy (15), from a practical standpoint the clinician must still rely solely upon an increased value for blood glucose to establish the diagnosis of diabetes mellitus. Because fasting hyperglycemia is now generally considered to represent a late manifestation of diabetes (9), the average physician will make the diagnosis of diabetes mellitus in a fasting euglycemic patient if he finds that results of the standard glucose tolerance test are abnormal. One should realize that the term "standard OGTT" is actually a misnomer, because at least 10 different authors and groups have given suggestions as to how an OGTT should be administered and interpreted (13). It is now believed by many (4-6, 9, 13) that most patients diagnosed as having diabetes on the basis of the currently accepted standards for an abnormal OGTT do not have diabetes mellitus and in all probability will never develop the disease.

Our study dealt with two issues. We believed that the reason for the current standard OGTT being unreliable was the variability in gastric emptying caused by the high osmolality of the glucose solution and that the high incidence of nausea and vomiting associated with the standard OGTT was due to delayed gastric emptying. Nausea and vomiting were completely eliminated when we used our modified OGTT, and we saw a much more rapid gastric emptying time (by nuclear scan) compared with the standard OGTT.

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Brener et al. (16), using different glucose concentrations, examined the regulation of gastric emptying of glucose. They found that, soon after the stomach was filled, glucose assumed a slow and calorie-constant emptying pattern such that 2.13 kcal of glucose were delivered per minute to the duodenum regardless of the amount or concentration of glucose administered. They described a "closed-loop" system in association with glucose ingestion and stated that a steady-state balance exists between the delivery of glucose to the duodenum and the inhibition of this delivery evoked from the duodenum by the glucose that enters it. We believe this theory explains why so many of the standard OGTTs give erratic results. Once the high osmolar glucose solution of the standard 100-g OGTT reaches the duodenum, gastric emptying is inhibited (thus creating a feeling of nausea). Regardless of the osmolarity of the solution, both the modified and the standard OGTT will deliver the same number of kilocalories to the duodenum per minute. Our modified OGTT delivered 1.92 kcal to the duodenum per minute, whereas the standard OGTT delivered 1.90 kcal/min, supporting the theory of Brener et al. (16) of the "closed-loop" system for glucose ingestion. Because in our modified OGTT the osmolarity of the solution was a third as great as that used in the standard OGTT, our solution emptied into the duodenum three times faster than the standard OGTT (4.5 vs 1.5 mL per minute). The modified OGTT is similar to commercial cola beverages in calorie content per milliliter, and we believe it is handled by the body in a much more physiological manner. We therefore believe that it is the osmolarity of the glucose solution that is the controlling factor for gastric emptying and for reliable, reproducible OGTTs.

Our nondiabetic volunteers consistently "peaked" their serum glucose concentrations at 30 min with the modified OGTT, whereas the diabetics consistently peaked at 60 min with the modified OGTT, even though our diabetic subject showed a more rapid gastric emptying. We believe that we can establish this as a recurrent trend with a larger population. Liddle et al. (17) described eight normal subjects who were given a 400-mL glucose solution containing 60 g of glucose to which 100 μCi of 99m Tc-SC had been added—a solution similar in osmolarity to our modified OGTT (0.83 mol/L). All of his normal subjects had a maximum value for serum glucose between 30 and 40 min and a lower glucose value after 60 min. Yalow et al. (18) found that patients with mild or early non-insulin-dependent diabetes mellitus often display a delay in insulin response followed by late hyperinsulinemia during oral glucose tolerance testing. This fact clearly explains why our nondiabetic patients (as well as Liddle's patients) peaked their serum glucose at 30 min (with a rapid insulin response) and why it took 60 min or longer for our type 2 diabetics to attain maximum values for, and then start decreasing, their glucose concentrations (a delay in insulin response). Our modified solution delivers glucose to the peripheral circulation serum at an initial rate greater than or equal to the standard OGTT. This should result in similar peak glucose values at 30 min for both the modified and the standard OGTT. However, the modified solution delivers a more compact bolus of glucose as compared with the standard OGTT, therefore allowing better differentiation between normal and abnormal insulin responses. With the modified OGTT, the tolerance curve for diabetics will have a different shape. We believe that our modified OGTT will allow faster and more accurate diagnosis of diabetes or prediabetes, with fewer side effects. Blood sampling may only be necessary at 0, 30, and 60 min after the modified glucose solution is ingested, to evaluate when the glucose "peaks" occurs and to establish a diagnosis. In normal individuals the peak value is at 30 min, in diabetics it is at 60 min or later.

We foresee that eventually the only bottled OGTT beverage will contain 50 g of glucose in 450 mL of flavored water. The new "standard" OGTT will then be a more nearly accurate, easily tolerated test.

References