The Diagnosis of Postprandial Hypoglycemia

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SUMMARY

Our observation that hypoglycemia, often self-diagnosed by our patients, was seldom confirmed led the authors to establish norms for the glucose tolerance test. We first obtained values for 650 patients who were entirely free from symptoms before and during testing. The median nadir in this group was 64 mg/dl. Ten percent of the patients had plasma glucose nadirs of 47 mg/dl or below and 2.5% had values of 39 mg/dl or less. Utilizing these values in combination with clinical criteria, we confirmed hypoglycemia after glucose load in 16 (median nadir 39.5 mg/dl) of 118 patients presenting with this diagnosis, and only 5 of the 16 were hypoglycemic after their usual meals. The other 102 patients, whose many complaints were unrelated to measured plasma glucose levels, had nadirs similar to those of the control group. Placebo tests performed on 14 nonhypoglycemic patients provoked symptoms (recorded by the patients themselves) that they considered indicative of hypoglycemia. Some accepted other diagnoses after we demonstrated that their symptoms occurred when they were normoglycemic. Since nadirs of hypoglycemics and control subjects overlap, we conclude that accurate diagnosis of hypoglycemia requires that symptoms develop concurrently with low blood sugar and that they are absent at other times. Low plasma glucose must be considered only one of the criteria in diagnosing functional hypoglycemia along with a relationship between food intake, timing of symptoms, correlation of symptoms and low glucose levels, and reproducibility of test results. DIABETES *30*:996–999, December 1981.

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Hypoglycemia following the ingestion of carbohydrates (termed reactive, functional, or postprandial by various authors) has long been recognized as a prevalent "nondisease".[1] Overdiagnosis of this rare condition results from failure to apply accepted diagnostic criteria. Laboratory test results add to the accurate evaluation of these patients, but functional hypoglycemia cannot be diagnosed by those means alone. One of several characteristic symptoms must be present such as sweating, hunger, palpitations, trembling, piloerection, and lightheadedness coincident with a low level of plasma glucose, lasting not more than an hour and subsiding as glucose levels rise.

In view of the importance customarily placed on laboratory criteria for the diagnosis of hypoglycemia, we have analyzed 650 glucose tolerance tests from patients who were asymptomatic in this respect and compared the results with those obtained from 118 patients referred for suspected hypoglycemia. Sixteen patients in the latter group who claimed to know the symptoms of hypoglycemia and when to expect them were given regular glucose tolerance tests and placebo tests.

MATERIALS AND METHODS

Subjects. Six hundred and fifty ambulatory patients analyzed for glucose tolerance presented no complaints suggestive of hypoglycemia after glucose loading or after their regular meals. This control group included 304 men and 346 women. Grouped by age, 29 were 18–20 yr, 156 were 21–30, 145 were 31–40, 162 were 41–50, 120 were 51–60, and 38 were over 60 yr. Although 14% of the patients were more than 20% overweight, their test values did not differ from those of the other group members. No patients in this group suffered from diabetes, impaired glucose tolerance, malignancy, liver disease, endocrine disease, or postgastrectomy syndrome. None was receiving steroids or birth control pills, and none had been referred for suspected hypoglycemia. These glucose tolerance tests were performed

as part of a diagnostic survey, often in routine yearly physical examinations of healthy persons. Some patients had diseases known not to affect the glucose tolerance test, such as chronic bronchitis, functional bowel syndrome, tension headaches, sinusitis, and spondylosis.

One hundred and eighteen patients suspected of having hypoglycemia underwent identical glucose tolerance tests. This group included 35 men and 83 women, of whom 6 were 18–20 yr, 17 were 21–30, 32 were 31–40, 24 were 41–50, 27 were 51–60, and 12 were above 60 yr. Sixteen were at least 20% overweight.

Sixteen of these patients with possible hypoglycemia received placebo as well as glucose tests. The patients selected for placebo testing had undergone one or more glucose tolerance tests elsewhere. The results in 14 patients indicated normalcy by our standards but had been interpreted as diagnostic of hypoglycemia. These patients were convinced that this diagnosis was accurate and were well read in the lay literature concerning this condition. They cited publications to support their beliefs and often presented complaints corresponding precisely to textbook descriptions. We told these patients that two tests with different sweeteners were needed for better correlation of their symptoms with blood sugar values. The nature of the tests and their order were known only to the treatment room nurse administering the glucose or placebo.

The glucose tolerance test. All patients to be tested for this study ate meals containing at least 200 g of carbohydrates a day for 3 days before testing. Venous blood samples were drawn before the test and 30, 60, 90, 120, 180, 240, and 300 min thereafter. Plasma glucose was determined using the Beckman glucose analyzer (Beckman Instruments, Fullerton, California).

The glucose load was given as caffeine-free cola (VWR Scientific Incorporated, San Francisco, California) containing 100 g of glucose, and the placebo drink was a diet preparation containing no carbohydrates. Patients were unable to distinguish between the two. Patients themselves recorded the times and types of their complaints in writing. Nurses in the treatment room observed the patients during all tests.

The hypoglycemic index was calculated as the drop of plasma glucose during the 90 min preceding the nadir divided by the nadir value.[2]

RESULTS

Nadirs of glucose tolerance tests in 650 controls. The times and values of those nadirs are presented in Table 1; frequencies of individual nadirs are presented in Figure 1. In these statistical compilations, the skew of the results is clear. Whereas the mean radir of 650 patients with no sign of hypoglycemia is 64.8 and the median is 64 mg/dl, the most frequently occurring low score (mode) is 75 mg/dl. The patients' nadirs are expressed as percentiles. The nadirs are as follows: 2.5th percentile 39 mg/dl, 5th percentile 43 mg/dl, 10th percentile 47 mg/dl, and 25th percentile 54 mg/dl. As noted, all patients remained asymptomatic during the testing. Among 17 patients with nadirs below the 2.5th percentile, 12 were women and 5 men. Twelve were under 30 yr, and 5 were between 31 and 50 yr. Figure 1 shows the frequency of various nadirs.

TABLE 1
Nadirs of glucose tolerance tests and their times in 650 controls

Time of nadir*	Number of patients (%)	Nadir in mg/dl		
		Mean	SD	Median
90 min	29 (4.5%)	68.7	19.94	65
120 min	58 (8.9%)	61.5	19.13	60
180 min	335 (51.5%)	63.4	15.67	57
240 min	189 (29.1%)	66.6	11.03	66
300 min	39 (6.0%)	69.2	12.14	71
Total	650 (100%)	64.8	14.87	64

* Interval between glucose loading and blood sampling.

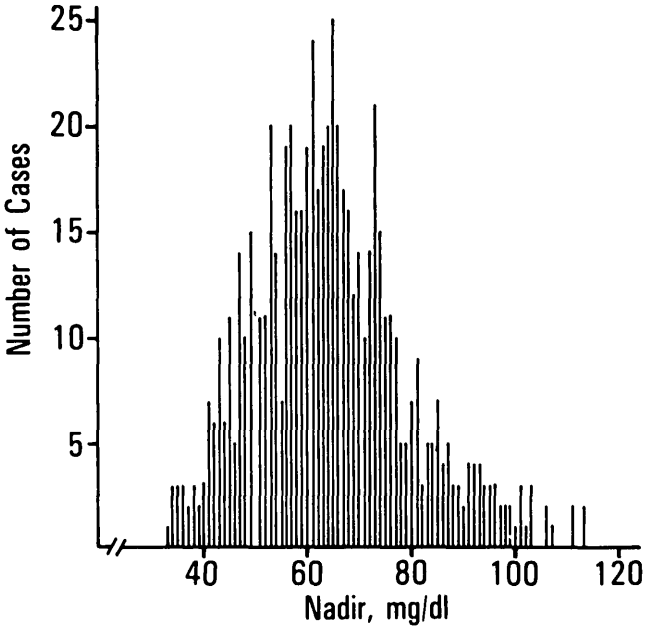


FIGURE 1. Frequency of various nadirs of glucose tolerance test in 650 asymptomatic patients. The median nadir was 64 mg/dl and the mode was 75 mg/dl.

Nadirs of glucose tolerance tests in patients suspected of hypoglycemia. Only 16 of 118 patients suspected of having hypoglycemia recorded symptoms typical of hypoglycemia that coincided with nadirs of plasma glucose. Twelve were women and four were men and all were over 40 yr. Their nadirs ranged between 33 and 48 mg/dl (mean 39.8 mg/dl, median 39.5 mg/dl). Eleven had nadirs below the 5th percentile and 8 of them were below the 2.5th percentile. Only 5 of these 16 patients with apparent postglucose hypoglycemia presented complaints following their regular meals. The others were asymptomatic at such times.

The remaining 102 patients included some who presented no complaints at the time of glucose tolerance testing and others with multiple complaints that were related neither to meals nor glucose loads and did not correlate with plasma glucose levels. This group included 71 women and 31 men. Their mean nadir was 61.3 mg/dl and the median was 64.3 mg/dl (no different from the control group, $P > 0.1$). Five patients had glucose nadirs below the 2.5th percentile, 8 below the 5th percentile, and 10 below the 10th percentile. Thirty were below the 25th percentile. This frequency distribution was not statistically different from that of the control group.

TABLE 2
Diagnoses of 118 patients with hypoglycemia

Reactive hypoglycemia*	
Symptomatic after glucose load and after meals	5
Symptomatic after glucose load only	11
Total	16
No clinical hypoglycemia	
Practically healthy†	14
Somatic problems‡	8
Bipolar or unipolar mood disorders	39
Somatization, anxiety	41
Total	102

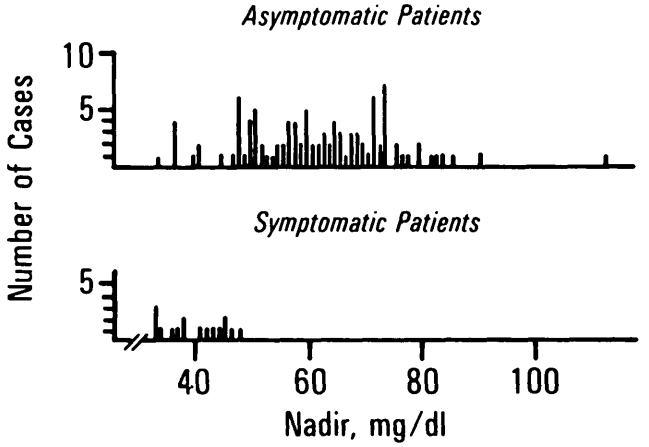
* Seven of the patients had no other problems, 5 were depressed, and 4 were somatizers.
† Past glucose tolerance tests done during routine check-ups were incorrectly interpreted in these asymptomatic patients.
‡ Meniere's syndrome, idiopathic hypertrophic subaortic stenosis, migraine, functional bowel disorder, mitral valve prolapse, factitious thyrotoxicosis, the symptoms of which had been incorrectly ascribed to hypoglycemia.

The clinical diagnoses of 118 patients suspected of hypoglycemia are categorized in Table 2. Individual data charting frequencies of nadirs in these potential versus reactive hypoglycemia patients are presented in Figure 2.

Glucose tolerance and placebo tests. Two patients presented complaints during nadirs of glucose tolerance testing and were, to their own surprise, completely asymptomatic during the placebo test. After the challenge with glucose, their nadirs were 36 and 38 mg/dl. These patients had true postprandial hypoglycemia. On follow-up, one was found to be completely asymptomatic for 1 yr, and the other for 2 yr, after testing on a diet free of concentrated simple carbohydrates.

The remaining 14 patients presented many and rather similar complaints during both tests. Their median plasma glucose values after glucose load were 95-155-139-100-74-76-86-90 mg/dl, and during placebo testing were 100-97-96-96-95-98-99-93 mg/dl. The many symptoms recorded during both regular glucose tolerance and placebo testing differed in those 14 patients who did not have true hypoglycemia.

FIGURE 2. Frequency of various nadirs of glucose tolerance test in 118 patients referred for having hypoglycemia. Above are 102 nonhypoglycemia patients. Below are 16 patients with reactive hypoglycemia after glucose load.



Along with complaints of perspiration, palpitation, and shaking (hunger was conspicuously absent), there were those of pressure in the head, yawning, numbness of the toes, back pains, difficulty in urinating, chills, among others. These did not correlate with low plasma glucose levels and often appeared during the first hour after the glucose load, persisting for hours and slowly tapering off if at all. Their plasma glucose nadirs were between 55 and 108 mg/dl with a mean of 81.8 and a median of 88 mg/dl. Complaints were similar after patients ingested glucose and the placebo. Often, the same symptoms were experienced at other times of the day, and for some patients, again on the following day.

In one of these patients the lowest glucose level during testing was 51 mg/dl and in all others it was above 57 mg/dl, i.e., well above the 10th percentile and the highest nadir in true hypoglycemic patients. Not surprisingly, all these patients had tried diets of various kinds without lasting benefit.

Hypoglycemic index. We calculated the hypoglycemic index, which correlated negatively with nadirs ($r = -0.541$; $P < 0.001$), for 325 asymptomatic patients. In 146 patients, the hypoglycemic index was above 0.8. In 16 patients with hypoglycemia after glucose load, the range was 0.83–3.67 with a median of 1.90. In 102 patients suspected of but not having hypoglycemia, the index was between 0.14 and 3.73. In 46 it was above 0.8, and in 10 it was even above the median (1.90) for the true hypoglycemic group. Therefore, the hypoglycemic index was found elevated in many asymptomatic patients.

DISCUSSION

Our results show that blood sugar values obtained in the routine glucose tolerance testing of asymptomatic patients had more frequent low values than was usually suspected. Ten percent of 650 patients had nadirs below 47 mg/dl. Patients coming for diagnostic study with a diagnosis of "hypoglycemia" made by various professionals and sometimes by themselves rarely showed clinical or laboratory evidence of hypoglycemia. The frequency distribution of their nadirs coincided with that of our control group. Postprandial hypoglycemia was found in only 5 of 118 patients who claimed to have this condition. Hypoglycemia after glucose load only was seen in 11 more patients.

In a large group of military draftees tested 2 h after glucose challenge, Fariss[3] found plasma glucose concentrations below 49 mg/dl in 7.4%, and below 29 mg/dl in 0.14%. Since most nadirs occur later than 2 h after glucose load, it is probable that their true incidence is even higher than Fariss reports. Hofeldt noted that 48% of normal subjects had nadirs below 50 mg/dl.[4] Occasionally, values as low as 35 mg/dl are found in healthy persons.[5,6] Clearly, considering nadirs below 50 mg/dl abnormal is a factor in the overdiagnosis of "hypoglycemia".[1,7] A plasma glucose level of 40–50 mg/dl can be tolerated easily by some people but it is disabling for others. The glucose tolerance test alone is not a reliable means of diagnosing reactive hypoglycemia.[8,9]

Although plasma glucose values are important, the diagnosis of reactive hypoglycemia is based primarily on clinical criteria. A low glucose nadir is only a confirmation and not diagnostic in itself. In support of this view, 8 of our patients who were hypoglycemic after glucose loading noted their symptoms during nadirs above the 2.5th percentile of our control subjects.

One of our patients experienced unusual symptoms. He suffered from arthritis of the hip with a sharp increase in pain after meals rich in sugar. He did not suspect he was hypoglycemic, but during glucose tolerance testing he recorded hip pain when his plasma glucose reached a nadir of 44 mg/dl. A low carbohydrate diet significantly decreased his pain during the 18 mo that he was followed.

Since all patients undergoing placebo testing had nadirs above the 10th percentile, the test was less valuable diagnostically than heuristically. These patients believed that, in the presence of "typical symptoms" of hypoglycemia, blood sugar levels were irrelevant. When helped to understand that their "typical symptoms" appeared during placebo testing while their plasma glucose levels were normal, they could at least consider other causes for their complaints.

The hypoglycemic index,[2] which is reputedly above 0.8 in all symptomatic patients, is said to be especially valuable for patients with nadirs below 65 mg/dl. Our results do not confirm the diagnostic validity of this index and lead us to conclude, with Johnson and others,[8] that the hypoglycemic index is of no value in the diagnosis of functional hypoglycemia.

In attempting to establish descriptive terminology for individuals in whom symptomatic hypoglycemia appeared after glucose load but was completely absent after usual meals, we suggest that such patients should be considered as having only *potential* reactive hypoglycemia. In this group of patients, symptomatic after glucose and asymptomatic after their usual meals, the median nadirs were 39 mg/dl after glucose load and 80 mg/dl after a normal meal. This indicates that the glucose tolerance test is an unphysiologic stress, seldom encountered outside the clinical laboratory. It is clear that a 100-g glucose load is a much stronger stimulus to insulin secretion and, therefore, is much more likely to provoke reactive hypoglycemia than any meal.[10,11]

Nevertheless, the 5-h glucose tolerance test is still widely used in the diagnosis of hypoglycemia. Although the upper limits of normal for glucose tolerance testing are standardized internationally, there is no agreement concerning the clinical significance of lower values obtained during testing. Moreover, it is important to realize that these values are skewed; therefore, the lower limit of the norm should be calculated not as the mean minus 2 standard deviations (such values are presented in Table 1 only for comparison with other published data), but as the 2.5th percentile, since the calculation of percentiles "has existed for many years and has impeccable credentials in both statistics and biology".[12]

On the basis of our observations, we conclude that functional hypoglycemia is a real but rare condition, confirmed in only 5 of 118 patients referred with this diagnosis. All five benefitted from a diet that was poor in refined carbohydrates. All had no symptoms after such meals. These true functional hypoglycemics are distinct from patients who develop hypoglycemic symptoms only after ingesting 100 g of glucose and who are mistakenly diagnosed by this criterion.

The diagnosis of functional hypoglycemia is accurate for patients who have no gastrointestinal abnormalities only if the following criteria are met: (1) symptoms appear 1½ to 5 h after the ingestion of mixed meals, (2) are coincident with low plasma glucose, (3) are reproduced during glucose tolerance testing, and (4) are absent when the patient is normoglycemic.

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