Comparison of Oral Glucose Tolerance Tests and Mixed Meals in Patients with Apparent Idiopathic Postabsorptive Hypoglycemia

Absence of Hypoglycemia After Meals

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SUMMARY

The relationship between symptoms of idiopathic postabsorptive hypoglycemia and glucose homeostasis was evaluated by giving oral glucose tolerance tests (OGTT) and mixed meals to 18 patients and 16 controls. Chemical hypoglycemia after OGTT occurred as often in patients referred because of possible hypoglycemia symptoms, 18 out of 80 (23%), as in controls, 4 out of 16 (25%). After glucose, patients showed both clinical and chemical hypoglycemia (mean ± SE plasma glucose, 48 ± 3 mg/dl), but insulin, glucagon, and growth hormone responses were similar to controls. After mixed meals, no chemical hypoglycemia occurred in patients (mean plasma glucose, 79 ± 3 mg/dl), yet 14 out of 18 (78%) had symptoms and/or signs consistent with hypoglycemia. No abnormality of glucose homeostasis was observed after meals that could account for symptoms or signs experienced by patients with idiopathic postabsorptive hypoglycemia. Since factors other than hypoglycemia appear to be involved, the disorder should be termed the idiopathic postprandial syndrome to avoid the connotation of chemical hypoglycemia. DIABETES *30*:465–470, June 1981.

There is considerable confusion concerning the pathogenesis and diagnostic criteria of idiopathic postabsorptive hypoglycemia.[1–14] It is generally agreed that the syndrome is associated with (1) repetitive, spontaneous symptoms or signs compatible with hypoglycemia 2–5 h after ingestion of mixed meals, (2) low circulating glucose levels after glucose ingestion in the absence of impaired glucose tolerance or altered proximal gastrointestinal tract function, and (3) reproduction of these symptoms or signs during chemical hypoglycemia after glucose ingestion. Isolated signs or symptoms suggestive of hypoglycemia after mixed meals are not diagnostic of idiopathic postabsorptive hypoglycemia, since they may be nonspecific. Isolated chemical hypoglycemia after oral glucose also cannot be accepted as evidence of idiopathic postabsorptive hypoglycemia, since similar results can occur in up to 48% of persons without repetitive spontaneous symptoms after mixed meals.[5,7,10–12] Chemical criteria for hypoglycemia after 75 or 100 g of oral glucose have not been standardized by any organized medical or scientific organization; however, most discussions of the subject focus arbitrarily on plasma glucose levels of 50–60 mg/dl.[3,5,7,10,11,13,14] An ad hoc committee on hypoglycemia composed of members from the American Medical Association, the American Diabetes Association, and the Endocrine Society listed no quantitative chemical criteria for postabsorptive hypoglycemia.[15] In an attempt to distinguish normals from patients, some investigators have suggested that a rise in plasma cortisol levels after clinical and chemical hypoglycemia is evidence of hypoglycemia sufficient to elicit pituitary-adrenal activation.[2,5–7,9] Unfortunately, any one or combination of the above tests is too variable to permit establishment of reliable criteria for a precise diagnosis of idiopathic postabsorptive hypoglycemia.

Since asymptomatic normal controls can have chemical hypoglycemia after OGTT, we suspected that the syndrome of idiopathic postabsorptive hypoglycemia may be unrelated to glucose homeostasis. We reasoned that most patients have postprandial symptoms (compatible with hypoglycemia) during their daily activities, which involve the ingestion of mixed meals rather than 75 or 100 g of glucose in solution. If chemical hypoglycemia were causally responsible for the symptoms that subjects experience in daily life, then one should be able to document chemical and clinical hypoglycemia 2–5 h after the ingestion of mixed meals. Therefore, we studied patients and controls after the ingestion of both glucose and mixed meals, measuring circulating concentrations of glucose, insulin, cortisol, glucagon, and growth hormone. In addition, we recorded symptoms

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and signs suggestive of hypoglycemia. Our results indicate that ingestion of mixed meals in the laboratory setting, although associated with symptoms and signs consistent with hypoglycemia 1–4.5 h after meals in 14 out of 18 (78%) patients, is unassociated with chemical hypoglycemia or significant abnormalities of the glucoregulatory hormones.

MATERIALS AND METHODS

Subject selection. Patients were selected consecutively as they were presented by referral to the Endocrine Clinic, Fitzsimons Army Medical Center. All prospective patients had spontaneous, repetitive symptoms 2–5 h after mixed meals consistent with chemical hypoglycemia, and thus were given 5-h oral glucose tolerance tests (OGTT). Eighty symptomatic individuals without a history of gastrointestinal disorders were studied. Since criteria to separate individuals into normal and abnormal groups are not available, we arbitrarily utilized the following criteria for diagnosis of abnormality: (1) a plasma glucose level less than 60 mg/dl during the OGTT, (2) symptoms or signs compatible with hypoglycemia during the test, and (3) a doubling of plasma cortisol 39–90 min after nadir of the plasma glucose. Of the 80 subjects, 18 were considered to have idiopathic postabsorptive hypoglycemia; they also received the mixed meal. The remaining 62 patients were biochemically normal or had impaired glucose tolerance; none were diabetic as recently defined.[16] Thus, the 18 patients studied in detail had spontaneous, repetitive symptoms 2–5 h after mixed meals during daily life that were reproduced during chemical hypoglycemia 3–5 h after OGTT. Their chemical hypoglycemia was associated with pituitary-adrenal activation. Sixteen nonobese age-, sex-, and weight-matched normal controls (Table 1) were randomly selected from paramedical personnel. None had symptoms suggestive of postabsorptive hypoglycemia. For purposes of this study, signs and symptoms of hypoglycemia after ingestion of mixed meals or glucose included palpitations, diaphoresis, piloerection, tremor, vasomotor instability, hunger, and headache. Each of these findings is well documented to result from hypoglycemia of other causes.[5,7–9] No patients or control subjects had impaired glucose tolerance or diabetes.[16] All control subjects and patients understood and signed informed consent forms before participation in accordance with the Human Use Committee at Fitzsimons Army Medical Center and the Health Services Command of the United States Army.

Procedures. Controls and patients were studied by oral glucose tolerance tests (OGTT, 100 g liquid oral glucose in the form of Pal-a-dex, J. T. Baker Diagnostics, Bethlehem, Pennsylvania) after 3 days of a 300-g carbohydrate diet. The solid meal consisted of 550 calories distributed as 48.3% carbohydrate (52 g), 26% fat, 21.7% protein, and 4% nonnutrient bulk (Figurines, Pillsbury, Minneapolis, Minnesota). The time interval between each test ranged from 3 to 8 wk. On the morning of testing, an indwelling scalp vein needle was inserted into an antecubital vein for ease of blood withdrawal. The patients were monitored by a physician or medical technician specifically trained in assessment of hypoglycemic signs and symptoms.

TABLE 1
Comparison of age, sex, and percent ideal body weight in patient and control subjects

	Patients	Control subjects	P value
Age	39.1 ± 2.4*	37.3 ± 2.6	NS
Sex	15 Women 3 Men	13 Women 3 Men	
% Ideal body weight	104 ± 3.2	105 ± 2.4	NS
Change of body weight between tests (kg)	0.6 ± 0.6	0.0 ± 0.5	NS

* Mean ± SE.

Laboratory tests. Plasma glucose determinations were performed using a Dupont Automatic Clinical Analyzer (Dupont Instruments, Wilmington, Delaware). Immunoreactive insulin was determined in serum by using human insulin standards and a pre-precipitated double antibody technique for separation of bound from free ^{125}I-insulin (Insulin Kit, Amersham, Arlington Heights, Illinois). Plasma immunoreactive glucagon was determined using Unger's 30-K antisera and charcoal to separate bound from free ^{125}I-glucagon.[17] ^{125}I-glucagon was prepared and purified as previously described.[19] Human growth hormone was determined in serum by radioimmunoassay using human growth hormone standards and a second antibody technique for separation of bound from free ^{125}I-growth hormone (Kallestad, Chaska, Minnesota). Cortisol levels were determined by radioimmunoassay (Solid Phase Cortisol Kit, Beckman, Fullerton, California).

Statistics. Areas under curves were calculated by the Triangulation method[19] using Hewlett-Packard Digital Computer 9830A, (Fort Collins, Colorado). Paired and unpaired comparisons were performed using Student's *t* test. Percent ideal body weight was calculated from the Metropolitan Life table.[20] Data are expressed as mean ± SE.

RESULTS

General. Characteristics of patients and controls are shown in Table 1. The change in weight between the two testing procedures was not significant. All 18 patients had signs or symptoms consistent with hypoglycemia (described above) after OGTT by definition; 14 out of 18 (78%) patients had similar signs or symptoms after mixed meals. In all patients and controls the timing of signs and symptoms occurred near the nadir of plasma glucose levels after oral glucose (Table 2). Four out of 16 (25%) normal control subjects also had appropriately timed signs and/or symptoms during hypoglycemia after OGTT, but no signs or symptoms were observed after mixed meals (Table 2). Pulse rates increases associated with hypoglycemia were not different in patients and controls 7 ± 3 beats/min versus 9 ± 4 beats/min (P = NS), respectively.

Oral glucose tolerance tests. After OGTT, plasma glucose, glucagon, cortisol, serum insulin, and growth hormone levels were determined in patients and controls. Mean basal glucose concentration (Figure 1) in patients and controls were not significantly different. To show that patients were distinct from the normal controls after OGTT, the mean glucose nadir in patients was 48 ± 2.0 mg/dl (range 29–60 mg/dl) whereas controls had a mean nadir of 60 ± 4.3 mg/dl (range 36–98 mg/dl, $P < 0.01$, Table 2).

To assess the pituitary-adrenal axis in response to chemical and clinical hypoglycemia, plasma cortisol levels were measured. In patients, the mean change from basal levels of

TABLE 2
Relationship of plasma glucose nadirs, time of glucose nadirs, and time of symptoms or signs after ingestion of glucose (OGTT) or mixed meals (MM) in patients and normal subjects

	Patients					Normal subjects				
	Glucose nadir (mg/dl)		Time of glucose nadir (min)	Time of symptoms or signs (min)		Glucose nadir (mg/dl)		Time of glucose nadir (min)	Time of symptoms or signs (min)	
	OGTT	MM	OGTT*	OGTT	MM	OGTT	MM	OGTT*	OGTT	MM
1	41	66†	270	240	210	69	80	120	None	None
2	59	74	300	300	210	98	86	210	None	None
3	38	91	210	180	180	81	78	90	None	None
4	50	79	210	180	210	76	88	240	None	None
5	47	86	240	240	150	36	77	180	None	None
6	51	91	240	240	180	41	66†	210	240	None
7	56	65†	240	240	60	62	60†	270	None	None
8	42	76	180	210	180	56	89	300	270	None
9	29	61†	180	180	210	60	69	210	None	None
10	46	82	240	240	270	61	77	180	None	None
11	55	88	270	270	120	73	95	300	None	None
12	59	83	270	270	None	33	80	180	180	None
13	37	78	180	180	None	59	75	180	None	None
14	53	83	300	300	270	58	83	60	None	None
15	57	78	270	240	180	58	75	300	None	None
16	51	82	210	210	None	44	77	180	210	None
17	52	85	270	300	120					
18	47	76	270	300	None					

* "Figurine" tolerance test omitted, since no true nadir was related to mixed meal.
† Each of these lowest glucose levels occurred 60 min after the meal ingestion.

cortisol 30–90 min after the onset of hypoglycemic signs or symptoms was 12.3 ± 1.2 μg/dl versus 9.8 ± 2.2 μg/dl in controls (P = NS). If the four controls who developed chemical hypoglycemia are excluded, the mean change from basal cortisol is 5.8 ± 3.6 μg/dl, which is lower than the mean patient data ($P < 0.05$). The cortisol peak occurred 30–90 min after chemical hypoglycemia in patients and controls. All patients, however, had greater than a twofold increase in plasma cortisol (selected for this trait) whereas only the four normals with chemical hypoglycemia had greater than a doubling of plasma cortisol.

Mean basal insulin level (Figure 2) in patients was 0.29 ± 0.03 ng/ml versus 0.34 ± 0.05 ng/ml in controls (P = NS). Insulin secretion expressed as area of total insulin secreted above basal after OGTT was 635 ± 74 ng/ml/300 min in patients and 568 ± 52 ng/ml/300 min in controls (P = NS). The mean rise in insulin level above basal after OGTT in patients was 4.9 ± 0.66 ng/ml versus 5.0 ± 0.66 ng/ml in controls (P = NS). The mean peak insulin values were not different in patients and controls (5.1 ± 0.67 ng/ml versus 5.3 ± 0.66 ng/ml; P = not significant). The insulin peaks occurred at similar times in patients (63.3 ± 4.8 min) and controls

FIGURE 1. Mean plasma glucose levels (± SE) after OGTT (solid lines) or mixed meals (dashed lines) in patients (closed circles) and controls (open circles).

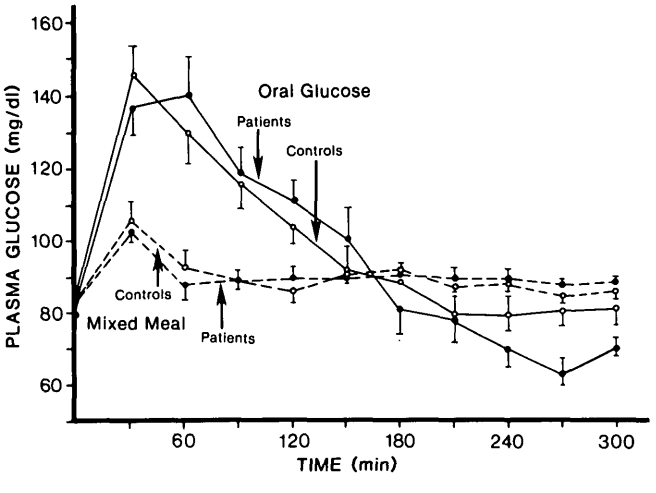
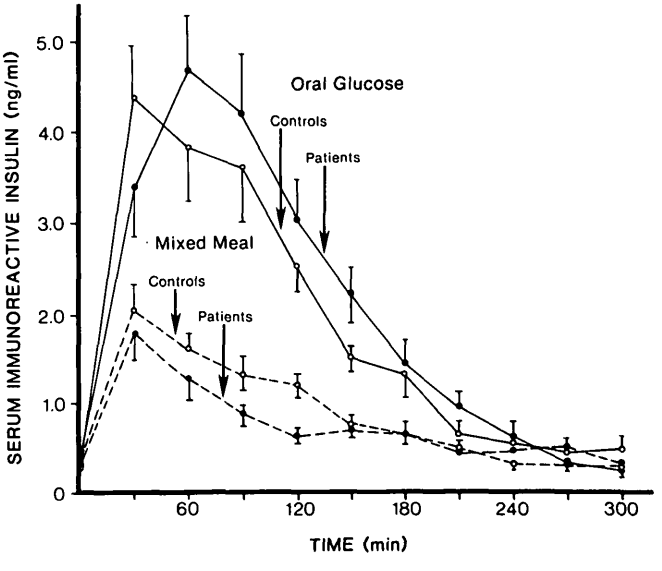


FIGURE 2. Mean serum IRI after OGTT or mixed meals in patients and control subjects. Symbols are described in Figure 1.



(52.5 ± 5.1 min; P = NS). The time from the glucose peak to the insulin peak was significantly greater in patients (25.3 ± 6.0 min) than in controls (9.4 ± 5.6 min; P < 0.05).

Basal glucagon levels were similar in both groups after the data from 3 patients with marked hyperglucagonemia were removed. These 3 patients had excessive large molecular weight glucagon species and are reported elsewhere (Charles et al., manuscript submitted for publication). Mean basal glucagon level in these 3 patients was 956 ± 276 pg/ml and no consistent alterations were observed after ingestion of oral glucose or mixed meals. For the remaining 15 patients, mean basal glucagon was 176 ± 29 pg/ml versus 171 ± 25 in controls (P = NS). The change from basal glucagon (Δ glucagon) after glucose (Figure 3) was similarly suppressed at 90, 120, and 150 min in both patients and controls (P < 0.05 for each time point). The mean glucagon nadir after OGTT in patients was 127 ± 27 pg/ml versus 105 ± 18 in controls (P = NS). The mean rise of glucagon from the nadir after hypoglycemia was 79 ± 10 pg/ml in patients and 41 ± 16 in controls (P < 0.03).

The mean basal growth hormone level in patients was 5.7 ± 2.1 ng/ml and 2.5 ± 0.6 in controls (P = NS). Growth hormone levels were suppressed similarly in both patients and controls between 30 and 150 min after glucose ingestion. Peak growth hormone responses in patients (16.3 ± 2.2 ng/ml) and controls (15.1 ± 1.4) and the rise in growth hormone after plasma glucose nadirs in patients (15.0 ± 2.0 ng/ml) and controls (14.7 ± 1.1) were similar. The growth hormone peak occurred later in patients (266 ± 7.2 min) than in controls (246 ± 8.4 min; P < 0.05).

Mixed meals. After mixed meals, plasma glucose, glucagon, cortisol, serum insulin, and growth hormone levels were determined in patients and controls. Mean basal glucose levels (Figure 1) before mixed meals were not significantly different from oral glucose tests. Patient mean plasma glucose nadir was 79 ± 2 mg/dl versus 78 ± 2 in controls (P = NS). The glucose nadir occurred at 242 ± 9 min in patients and at 201 ± 18 min in controls (P < 0.05).

In patients the mean change from basal cortisol was 4.1 ± 0.64 μg/dl versus chemical hypoglycemia, cortisol changes could not be correlated with plasma glucose nadirs.

Mean basal insulin levels (Figure 2) before mixed meals were 0.39 ± 0.05 ng/ml and 0.31 ± 0.05 in patients and control subjects, respectively (P = NS). Insulin secretion, expressed as mean area of total insulin secreted above basal after mixed meals, was 285 ± 27 ng/ml/300 min in patients and 225 ± 22 in controls (P = NS). The mean rise in insulin level above basal after meals in patients was 1.8 ± 0.24 ng/ml versus 1.9 ± 0.26 in controls (P = NS). The mean peak insulin value in patients was 2.2 ± 0.2 ng/ml versus 2.2 ± 0.3 in controls, and both values occurred at similar times (P = NS).

Excluding the 3 patients with elevated large molecular weight glucagon species, the mean basal glucagon levels (Figure 3) before mixed meals was 133 ± 19 pg/ml in patients and 164 ± 19 in controls (P = NS). The mean rise of glucagon from basal after meals in patients was 45 ± 9 pg/ml versus 50 ± 14 in controls (P = NS). Glucagon levels after mixed meals were stimulated at 30, 90, 120, 150, and 210 min in patients and at all sampling times in controls (Figure 3; P < 0.05 for each time point). The mean plasma glucagon level was significantly lower in patients than in controls at 180 min (P < 0.01), 240 min (P < 0.04), and 270 min (P < 0.03) after mixed meals. Glucagon secretion above basal, calculated as the area under the curve after mixed meals, was significantly lower in patients (4.84 ± 1.9 ng/ml/300 min) than in controls (10.1 ± 2.4 ng/ml/300 min; P < 0.05).

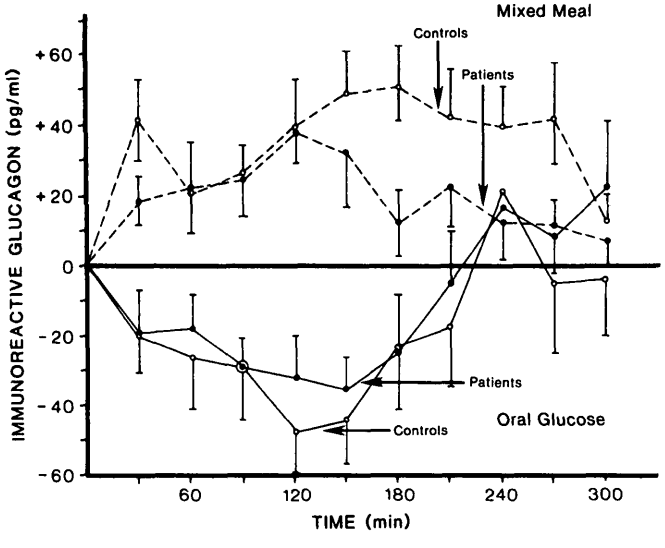
Mean basal growth hormone levels before mixed meals were 3.78 ± 0.68 ng/ml in patients and 3.35 ± 0.79 in controls (P = NS). Six patients and 10 controls had growth hormone rises after mixed meals. There was no difference between the peak levels or rise above nadir in these patients and controls, and the rises occurred at similar times.

Comparison of OGTT and mixed meals. Glucose levels at nadir were 29 mg/dl and 22 mg/dl below mean basal levels in patients and controls, respectively, after glucose (P < 0.05). Patient and control glucose nadirs were considerably lower after glucose than after mixed meals (P < 0.001). No chemical hypoglycemia was observed after mixed meals in either group, yet 14 out of 18 patients (78%) had signs or symptoms compatible with hypoglycemia that were similar to those experienced after OGTT. Consistent with the absence of chemical hypoglycemia, rises in plasma cortisol were not observed after mixed meals in either patients or controls.

Insulin secretion, expressed as area of total insulin secreted above basal, was greater after glucose than after mixed meals in both patients and controls (Figure 2, P < 0.003).

The mean peak growth hormone levels after oral glucose in patients and controls were significantly higher than the mean peak levels of patients or controls after mixed meals (P < 0.003). The mean rise of growth hormone above basal was also significantly higher after OGTT than after mixed meals in both groups (P < 0.004). The peak growth hormone level was achieved earlier after OGTT than after mixed meals in both patients (P < 0.05) and controls (P < 0.008).

FIGURE 3. Mean change in plasma IRG from basal values after OGTT or mixed meals in patients and controls. Symbols are described in Figure 1.



DISCUSSION

The primary goal of this study was to assess whether or not patients with idopathic postabsorptive hypoglycemia had abnormal glucose homeostasis appropriately associated with hypoglycemia signs or symptoms after mixed meals. The results show that after the ingestion of mixed meals by patients, plasma glucose levels are not abnormally low even though signs and symptoms consistent with hypoglycemia developed in 14 out of 18 (78%). Further, cortisol rises were not observed after meals, suggesting that these signs and symptoms are unassociated with hypothalamic-pituitary-adrenal activation. None of the controls had symptoms consistent with hypolgycemia during their daily life, yet 4 out of 16 (25%) had both clinical (symptomatic) and laboratory (chemical hypoglycemia and elevated cortisol) findings consistent with hypoglycemia after OGTT. Of the 80 patients referred to our clinic, 18 (23%) had clinical and laboratory findings consistent with idiopathic postabsorptive hypoglycemia after OGTT.

The observations that (1) chemical hypoglycemia does not occur after mixed meals in patients even though appropriately timed symptoms persist, (2) the same prevalence (23–25%) of chemical hypoglycemia occurred in patients referred to our clinic and in randomly selected normal control subjects, and (3) glucoregulatory hormones measured in this study are similar in patients and controls after both OGTT and mixed meals, strongly suggest that idiopathic postabsorptive hypoglycemia is unrelated to a specific measurable defect of glucose homeostasis using the described technology. Alternative explanations as to why glucose homeostasis appears normal in the current study when compared with earlier work are that (1) prior studies may have included obese subjects or selected control subjects, (2) inappropriate testing procedures were used (e.g., large quantities of oral glucose), or (3) more sophisticated tests may be required, such as measurement of neuroglycopenia or glucose utilization by specific neural centers.

To insure that the mixed meal was of sufficient caloric input, 5 patients were also given 825-cal meals. The glucose nadirs and hypoglycemic signs and symptoms were similar to the 550-cal meal (data not shown). To determine if the mixed meal could induce chemical hypoglycemia, one patient with a history of a Billroth II procedure and chemical (35 mg/dl) and clinical hypoglycemia 90 min after OGTT ingestion was also studied. After the 550-cal meal, he developed chemical hypoglycemia (51 mg/dl) associated with greater than a doubling of plasma cortisol and hypoglycemic symptoms and signs. Thus, the meal used in this study was sufficient to elicit chemical hypoglycemia and pituitary-adrenal activation.

Although glucoregulatory hormones have been difficult to assess in some prior reports, the current study describes data obtained from patients and controls that were matched for weight, age, and sex. No patients or controls were obese. Further, this trial was prospective in that patients were studied and selected as they presented in a consecutive manner, rather than by random or prior selection. The matching of patients and controls may explain insulin secretory disimilarities observed in this study when compared with other reports.[1–3] The 25% prevalence of chemical hypoglycemia after OGTT in control subjects is expected;[10–12] the reason similar findings are not observed in other studies is unclear, but may be related to control subject selection.

Although it has been implied that the rate of change of glucose is causally related to hypoglycemic symptoms and release of counterregulatory hormones,[4] this does not apply to our subjects, since controls and patients had similar changes in glucose levels after mixed meals. Controls also had an earlier glucose nadir with similar peak glucose times, further suggesting that rate of glucose fall was not of importance in this study.

The data presented do not support the concept that chemical hypoglycemia is causally related to symptoms experienced after mixed meals. These data may also explain why there is controversy in choosing criteria for the diagnosis of idiopathic postabsorptive hypoglycemia using OGTT, since individuals with the idiopathic postprandial syndrome have virtually identical results as normal controls.

We suspect that if an idiopathic postprandial syndrome exists, it is not related to factors such as glucose, cortisol, insulin, glucagon, or growth hormone in the patients presented (catecholamine levels were not measured in our study). The fact that patients had lower glucagon responses to mixed meals when compared with controls does not directly relate to postabsorptive hypoglycemia because during this test, glucose levels were similar in both groups. The only objective data separating normals from idiopathic postprandial syndrome patients in this study are that a nonrandom distribution of patients with hyperglucagonemia were observed in the patient group.

In conclusion, we suggest that patients who have signs or symptoms suggestive of the idiopathic postprandial syndrome in daily life be evaluated *not* by liquid oral glucose testing (OGTT), but rather by mixed meals. This conclusion has profound implications in the cost effectiveness of health care delivery and research. If a patient experiences daily signs or symptoms consistent with hypoglycemia in the absence of chemical hypoglycemia after mixed meals, then the patient can be treated with counselling, multiple feedings, and/or drugs if required.[7] Most importantly, the patient should be informed that chemical hypoglycemia as measured may not be involved in this disorder. We further suggest that the pathogenesis of symptoms in this idiopathic postprandial syndrome may be related to gastrointestinal circulatory dynamics or hormone responses after meals in a specific subgroup of otherwise normal subjects.

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REFERENCES

[1] Luyckx, A. S., and Lefebvre, P. J.: Plasma insulin in reactive hypoglycemia. Diabetes *20*:435–42, 1971.

[2] Hofeldt, F. D., Lufkin, E. G., Hagler, L., et al.: Are abnormalities in in-

sulin secretion responsible for reactive hypoglycemia? Diabetes *23*:589–96, 1974.

[3] Lefebvre, P. J., Luyckx, A. S., and Lecomte, M. J.: Studies on the pathogenesis of reactive hypoglycemia: role of insulin and glucagon. Horm. Metab. Res. *8* (Suppl. 6):91–98, 1976.

[4] DeFronzo, R. A., Andres, R., Bledsoe, T. A., Boden, G., Faloona, G. A., and Tobin, J. D.: A test of the hypothesis that the rate of fall in glucose concentration triggers counter-regulatory hormonal responses in man. Diabetes *26*:445–52, 1977.

[5] Hofeldt, F. D.: Reactive hypoglycemia. Metabolism *24*:1193–1208, 1975.

[6] Hofeldt, F. D., Adler, R. A., and Herman, R. H.: Postprandial hypoglycemia fact or fiction? JAMA *233*:1309, 1975.

[7] Permutt, M. A.: Postprandial hypoglycemia. Diabetes *25*:719–36, 1976.

[8] Yager, J., and Young, R. T.: Non-hypoglycemia is an epidemic condition. N. Engl. J. Med. *291*:907–08, 1974.

[9] Cahill, G. F., Jr., and Soeldner, J. S.: A non-editorial on non-hypoglycemia. N. Engl. J. Med. *291*:905–906, 1974.

[10] Jung, Y., Khurana, R. C., Corredor, D. G., et al.: Reactive hypoglycemia in women. Diabetes *20*:428–34, 1971.

[11] Fariss, B. L.: Prevalence of post-glucose-load glycosuria and hypoglycemia in a group of healthy young men. Diabetes *23*:189–91, 1974.

[12] Abell, D. A., and Beischer, N. A.: Evaluation of the three-hour oral glucose tolerance test in detection of significant hyperglycemia and hypoglycemia in pregnancy. Diabetes *24*:874–80, 1975.

[13] Ensinck, J. W., and Williams, R. H.: Disorders causing hypoglycemia. *In* Textbook of Endocrinology. Williams, R. H., Ed. Philadelphia, W. B. Saunders, 1974, pp. 627–59.

[14] Bleicher, S. J.: Hypoglycemia. *In* Diabetes Mellitus: Theory and Practice. Ellenberg, M., and Rifkin, H., Eds. San Francisco, McGraw-Hill, 1970, pp. 958–89.

[15] Ad Hoc Committee on Hypoglycemia: Statement on hypoglycemia. Arch. Intern. Med. *131*:591, 1973.

[16] National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes *28*:1039–57, 1979.

[17] Gerich, J. E., Charles, M. A., and Grodsky, G. M.: Characterization of the effects of arginine and glucose on glucagon and insulin release from the perfused rat pancreas. J. Clin. Invest. *54*:833–41, 1974.

[18] Greenwood, F. S., Hunter, W. N., and Glover, J. A.: The preparation of 131-I labeled human growth hormone of high specific radioactivity. Biochem. J. *89*:114–16, 1963.

[19] Ostle, B.: Measurement Data in random Sampling Distributions in Statistics. Iowa, Iowa State College Press, 1954, pp. 40–63.

[20] Bray, G. A.: Who are the obese? *In* The Obese Patients, Vol. IX, Major Problems in Internal Medicine. Smith, L. H., Jr., Ed. Philadelphia, W. B. Saunders, 1976, p. 8.