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Evaluation of a standardized hyperglucidic breakfast test in postprandial reactive hypoglycaemia

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Summary The oral glucose tolerance test is not specific for diagnosing postprandial reactive hypoglycaemia, since it too frequently induces low blood glucose values in subjects who have never complained of symptoms of this. By contrast, the mixed meal tests are deceptive for this purpose because they do not induce hypoglycaemia in subjects who have complained of of hypoglycaemic symptoms. We investigated the frequency of hypoglycaemia after a standardized hyperglucidic breakfast test in three groups of subjects:group A, 43 control subjects; group B, 38 postprandial reactive hypoglycaemic patients; group C, 1193 asymptomatic subjects undergoing assessment of glycoregulation. In the 38 subjects with suspected reactive hypoglycaemia the mean blood glucose nadir was 3.48 ± 0.08 mmol/l, i.e. lower than in control subjects (4.83 ± 0.13 $p < 0.0001$). Blood glucose levels less than 3.3 mmol/l were found in 47.3 % of subjects with suspected postprandial reactive hypoglycaemia (group B), i.e more frequently than in control subjects (group A: 2.2 % $p = 1.6 \times 10^{-6}$) and asymptomatic subjects (group C: 1 % $p = 8 \times 10^{-22}$). This markedly higher frequency of low blood glucose values in subjects with postprandial symptoms compared with control and asymptomatic subjects suggests that this test detects a tendency to hypoglycaemia after a standardized hyperglucidic breakfast. Since this test mimics average French eating habits, the results suggest that the patients undergo such symptoms in their everyday life, and that the hyperglucidic breakfast test is a simple alternative to ambulatory glucose sampling for diagnosis of postprandial reactive hypoglycaemia. [Diabetologia (1995) 38: 494–501]

Key words Mixed meal, oral glucose tolerance test, reactive hypoglycaemia.

Postprandial reactive hypoglycaemia (PRH) is a controversial syndrome, since its symptoms are not specific and correlate weakly with blood glucose concentrations measured after a glucose load [1, 2]. The syndrome cannot be diagnosed unless the correct criteria are applied [3]. The classic oral glucose tolerance test (OGTT) is frequently used by physicians to diagnose this condition; however, this has been demonstrated to be unreliable in this context, since blood glucose often decreases below the starting values in the late phases of this test, even in subjects with no history of PRH. For example Lev Ran and Anderson [5] reported that 25 % of patients with no signs of PRH reached values lower than 3 mmol/l. Chemical hypoglycaemia may occur as often in control subjects as in patients referred because of possible hypoglycaemic symptoms [5, 6]. Thus, a low blood glucose value during OGTT does not mean that the subject is prone to hypoglycaemia in everyday life [4]. Consensus conferences have emphasized that this diagnosis should not be made by OGTT but by the measurement of a low blood glucose value observed simultaneously with the signs of the syndrome [3]. Ambulatory blood glucose control [7] is a satisfacto-

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Abbreviations: PRH, Postprandial reactive hypoglycaemia; OGTT, oral glucose tolerance test.

ry solution and has been used successfully. It has shown that 46 % of a group of 28 patients with this complaint did have blood glucose values lower than 3.3 mmol/l during postprandial symptoms. Moreover, 18 %had glycaemia lower than 2.8 mmol/l. Unfortunately, this procedure is difficult to perform under routine conditions. A possible alternative would be a standard mixed meal reproducing the normal nutritional habits of the subjects: if hypoglycaemia could be induced, it could be concluded that the subject may experience hypoglycaemia during their everyday life. Unfortunately, some trials with standard mixed meals have given unreliable results [5, 8, 9], leading to the conclusion that these patients do not experience hypoglycaemia after such a meal. Since PRH can be prevented with a diet correcting excessive carbohydrate intake [10], we hypothesized that the meals used in these studies were too equilibrated, and to some extent compensate for the abnormality responsible for hypoglycaemia; therefore the test was unable to detect the disease. A more 'hyperglucidic' standardized breakfast, which could both mimic the French nutritional habits and represent a strong glucose stimulus, might avoid some pitfalls of both the OGTT and the too- equilibrated mixed meals for this purpose. Thus, our working hypothesis was that PRH is not infrequent, but an adequate tool for diagnosis is still missing. If a subject underwent an exaggerated fall in blood glucose after such a breakfast, it would be reasonable to assume that they may suffer from a similar fall (with its clinical symptoms) during everyday life.

Subjects and methods

Subjects. Two groups of subjects were compared in this experiment. Group A, 43 volunteer control subjects of normal weight (9 males and 34 females; age: 23 to 49 years; weight: 55–77 kg; height: 156–179 cm); group B, 38 subjects with suspected PRH reporting two or more of the postprandial signs listed in the questionnaire presented in this paper (4 males, 34 females; age: 20–54 years.; weight: 48–85 kg; height: 146–173 cm). None of the subjects in either group were taking medication at the time of the investigation. In addition, we had the opportunity to perform the hyperglucidic breakfast test in a large series of subjects who came to our outpatient unit for a nutritional check-up in which this test was used to assess glycoregulation. These subjects attended for dietary counselling due to moderate obesity. A group of such subjects was selected and referred to as group C. They consisted of 1193 subjects with no symptoms suggestive of PRH (473 males and 720 females; age, 17–62 years; weight, 50–89 kg; height, 154–181 cm). For all groups pituitary, thyroid, and adrenal causes of hypoglycaemia were excluded. No patient had insulinoma or either partial or total gastrectomy. Markedly obese subjects (body mass index > 31 kg · m^{-2}) and patients with impaired glucose tolerance according to the World Health Organization criteria were excluded from the study. Exclusion of glucose tolerance abnormalities was made by previous OGTT or blood glucose measurements if they were available, or from the results of the breakfast test. All subjects gave their informed consent.

Hyperglucidic breakfast test. No dietary restriction was imposed; however, subjects were asked to fast for 12 h before starting the test at 8.30 hours. A cannula for blood sampling was placed in the cephalic vein at the level of the cubital fossa. The subjects ate the standardized breakfast which was composed of bread (80 g), butter (10 g), jam (20 g), skimmed concentrated milk (80 ml) (Gloria SA, Paris, France), sugar (10 g) and powdered coffee (2.5 g). The breakfast thus comprised 2070 kilojoules with 9.1 % protein, 27.5 % lipid, and 63.4 % carbohydrate. The average time for consuming the meal was 6 min. Blood samples were taken twice before the meal and at 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300 min following the start of the meal. A preliminary blood glucose evaluation at each of these times was made with a glucose analyser (glucometer 3; Ames Bayer Diagnostics, Puteaux, France). If a tendency to a fall in blood glucose was detected, patients were observed more closely for onset of symptoms. If blood glucose levels at the end of the test were still decreasing, blood continued to be drawn every 30 min until levels returned to baseline. An investigator remained with the patient and if hypoglycaemic symptoms were mentioned, they were noted on a questionnaire (and compared to the signs reported to occur spontaneously) and an additional blood sample was taken.

Comparison between the hyperglucidic breakfast test and a classic mixed meal. An equilibrated mixed meal was compared to the hyperglucidic breakfast. Its composition was calculated to correspond to the average of the three breakfast tests described in the literature which have not been shown to induce hypoglycaemia in patients referred for suspicion of PRH [5, 8, 9]. This breakfast comprised bread (40 g), two eggs, powdered skimmed milk (14.5 g, SACM, Hochfelden, France which is composed of 14 % fat, 31 % protein and 43.2 % lactose), sugar (5 g) and rice krispies (25 g, comprising 86 % carbohydrates, 6 % proteins, and 1 % lipids). The breakfast thus comprised 2030 kilojoules with 21.4 % protein, 30.3 % lipids, and 48 % carbohydrates. Blood was drawn twice before the meal and at 15, 30, 60, 90, 120, 150, 180 min following the start of the meal. This test was compared with the hyperglucidic breakfast described above in six healthy subjects (three males, three females, age 22–26 years, height 170–174 cm; weight 57–65 kg). Tests were performed at random order with a 1-week interval.

Questionnaire. A standardized questionnaire for symptoms of hypoglycaemia according to the symposium of Rome [3] was presented to the subject if he/she mentioned postprandial symptoms. The symptoms occurring in everyday life were also asked for, and compared to symptoms occurring during the breakfast test. We looked for signs of neuroglucopenia: blurred vision, headache, confusion, depression, paraesthesia; and sympathetic signs: tremours, anxiety, hunger, palpitations, sweating, nausea, dizziness and weakness. Patients were asked to score all these symptoms from 0 to five, five being the most severe.

Laboratory measurements. All samples were analysed for plasma insulin by a radioimmunoassay (kit SB-INSI-1 from Sorin Biomedica, Saluggia, Italy) and plasma glucose with a Beckman glucose analyser (Beckman Instruments, Brea, Calif., USA). The within assay coefficient of variation (CV) for insulin was determined by repeated measurements of the same sample and was between 8.6 % (low values) and 9.7 % (high values). The between assay CV for insulin was between 12.5 % (low values) and 14.4 % (high values). The sensitivity (lowest detectable value) was 2 μU/ml.

Homeostasis model assessment (HOMA). An attempt to evaluate insulin sensitivity and beta-cell responsiveness was made with the homeostasis model assessment (HOMA), a simple

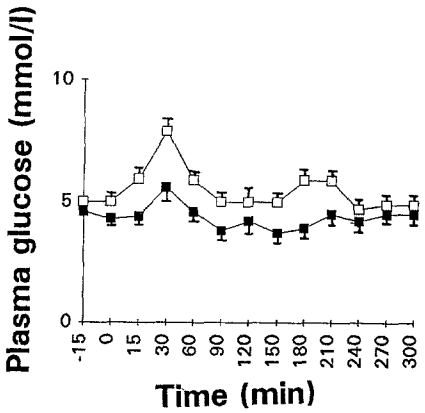

Fig. 1. Blood glucose response to the breakfast tolerance test in patients referred for postprandial hypoglycaemia (group B, $n = 38$, lower curve) compared to 43 control subjects (group A). Values given as mean ± SEM. No significant difference between groups

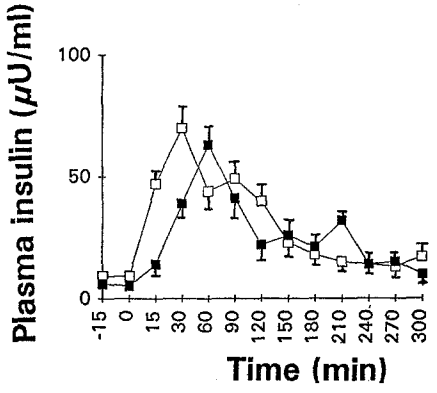

Fig. 2. Insulinaemic response to the breakfast tolerance test. Group A (43 control subjects) □; group B (38 subjects with symptoms of postprandial reactive hypoglycaemia) ■.Values given as mean ± SEM. No significant difference between the two groups

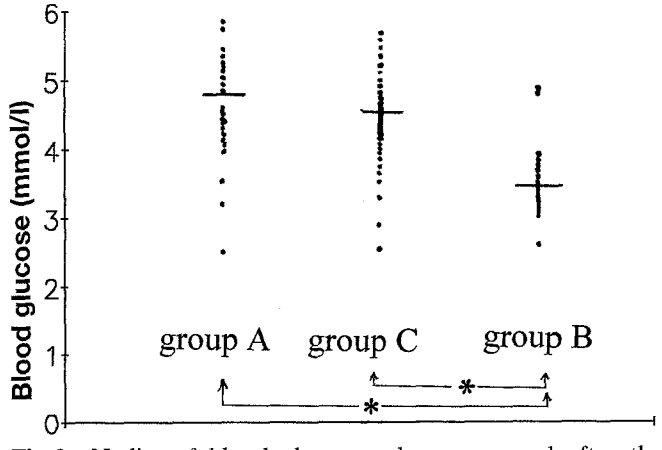

Fig. 3. Nadirs of blood glucose values measured after the hyperglucidic breakfast test in groups A (control subjects), B (suspicion of postprandial reactive hypoglycaemia) and in an additional goup C of 1193 patients with no postprandial signs. The 38 subjects of group B have a lower mean blood glucose nadir than the other groups (*$p < 0.0001$)

calculation which has been validated in comparison with the euglycaemic clamp [11]. The insulin resistance index is defined as insulin/($22.5e^{-\ln \text{glucose}}$) and beta-cell function is equal to 20 × insulin/(glucose-3.5 mmol/l). The lowest of the two baseline values before the breakfast test was employed for this calculation.

Statistical analysis

All data are expressed as means ± SEM. Statistical analyses employed one-way analysis of variance (ANOVA) to ascertain significance among multiple means, with the Newman-Keuls interpretation of individual significant effects. Frequency comparisons were performed with Fisher's exact test. The null hypothesis was, as usual, rejected for p values of less than 5 %.

Results

Response to the breakfast tolerance test. Glycaemic and insulinaemic responses in the groups A and B during the breakfast tolerance test are shown on Figures 1 and 2. Insulin responses were not significantly different. Blood glucose responses on the whole did not exhibit significant differences, but there was a non-significant tendency to find lower blood glucose values in group B, i.e. subjects investigated for postprandial symptoms.

Blood glucose nadirs during the test. In the 38 subjects explored for suspected reactive hypoglycaemia the mean nadir of glycaemia was 3.48 ± 0.08 mmol/l, i.e. lower than in control subjects (4.83 ± 0.13 $p < 0.0001$), as shown in Fig. 3.

Time at which insulin and glucose peaks and nadirs occur. The glucose peak occurred at a mean time of 43.42 ± 5.24 min in group A (control subjects) and at 35.55 ± 2.21 min in group B (suspicion of PRH). In group C (1193 asymptomatic patients), this peak was found at 45.6 ± 0.77 min. There was no difference between A and B, or between A and C, but this peak occurred significantly earlier in B than in C ($p < 0.03$). The lowest blood glucose value occurred at a mean time of 165.62 ± 3.65 min in group A and at 171.15 ± 8.31 min in group B. However, it occurred at 160.91 ± 1.16 min in group C. There was no statistically significant difference among these times. The highest insulin value occurred at a mean time of 61.15 ± 4.79 min in group A and at 67.22 ± 6.33 min in group B. For comparison it occurred at 71.667 ± 1.67 min in group C. These times were not different.

Frequency of low blood glucose values in the three groups. As shown in Table 1, frequency of blood glucose lower than 2.8 mmol was not different in the

Table 1. Frequency of low blood glucose level nadirs during the hyperglucidic breakfast test in the three groups of subjects of the study

	Blood glucose nadir	
	< 2.8 mmol	< 3.3 mmol
Control subjects ($n = 43$)	1 (2.2 %)	1 (2.2 %)[a]
Signs of hypoglycaemia ($n = 38$)	1 (2.6 %)	18 (47.3 %)
No sign of hypoglycaemia ($n = 1193$)	1 (0.08 %)	12 (1 %)[b]

Comparison (Fisher's exact test). [a] Group B (suspected hypoglycaemia) vs control subjects: $p = 1.6 \times 10^{-6}$; [b] group B (suspected hypoglycaemia) vs subjects explored for a routine check-up of glycoregulation without any complaint of postprandial signs: $p = 8 \times 10^{-22}$

three groups. In group B (subjects with suspicion of PRH $n = 38$) there was only one case (2.6 %); in group A (control subjects $n = 43$) only one (2.2 %) and in group C (asymptomatic subjects $n = 1193$) only one (0.08 %). There was no statistical difference among these three groups. Frequency of blood glucose levels lower than 3.3 mmol was as follows. In group B ($n = 38$) there were 18 cases (47.3 %); in group A ($n = 43$) only one (2.2 %) and in group C ($n = 1193$) 12 (1 %). There was no difference between group A and group C in frequency. By contrast subjects from group B (suspicion of hypoglycaemia) had a significantly higher frequency of blood glucose values lower than 3.3 mmol/l than either group A ($p = 1.6 \times 10^{-6}$) or group C ($p = 8 \times 10^{-22}$).

Homeostasis model assessment. The homeostasis model assessment showed a lower insulin resistance index (i.e. a higher insulin sensitivity) in group B than group A (1.71 ± 0.13 vs 2.29 ± 0.74, $p < 0.01$). The beta-cell function index was lower in B (185.3 ± 20.39) compared to A (278.72 ± 27.14, $p < 0.01$).

Hypoglycaemic symptoms during the test. Frequency of symptoms in the questionnaire was assessed in groups A and B. In A (control subjects), no symptoms were noted on the questionnaire. In group B 10 subjects noted symptoms on the standardized list, i.e. an occurrence of symptoms markedly lower than the frequency of low blood glucose values ($p = 6.37 \times 10^{-2}$), but a significantly higher frequency than in group A ($p = 5.03 \times 10^{-4}$). Among signs of neuroglucopenia, headache (once) and paraesthesias (twice) were reported. Among sympathetic signs, anxiety (twice), hunger (four times), palpitations (once), sweating (once), nausea (once), dizziness (twice) and weakness (twice) were noticed.

Comparison between the hyperglucidic breakfast and the classic mixed meal (Table 2). Comparison of blood glucose and insulin values over the 180 min fol-

Table 2. Comparison of blood glucose and insulin responses to a hyperglucidic breakfast test vs a classic mixed meal

		Time (min)									
		− 15	0	15	30	60	90	120	150	180	
Insulinaemia (μU/ml)	Hyperglucidic breakfast	7.5 ± 0.9	8.2 ± 0.9	26.7 ± 5.9	54.7 ± 17.6	36.3 ± 8	24.3 ± 7.7	19.3 ± 5.3	18 ± 3.5	13.2 ± 3.2	
	Mixed breakfast	9.5 ± 1.1	10.3 ± 1.6	16.8 ± 2.8	38.3 ± 4.6	34.5 ± 4.1	27.7 ± 7	24 ± 5.4	20.3 ± 3.4	12.4 ± 1.5	
Blood glucose	Hyperglucidic breakfast	5 ± 0.1	4.8 ± 0.1	5.7 ± 0.2	7 ± 0.3	5.6 ± 0.5	5 ± 0.2	4.6 ± 0.2	4.8 ± 0.1	4.8 ± 0.3	
	Mixed breakfast	5 ± 0.3	4.9 ± 0.3	5 ± 0.2	6.5 ± 0.5	5.2 ± 0.5	4.6 ± 0.4	4.7 ± 0.3	4.7 ± 0.2	4.7 ± 0.1	
Incremental insulin above baseline	Hyperglucidic breakfast	0.67 ± 1.22		18.17 ± 5.96	46.5 ± 17.4	28.17 ± 7.84	16.17 ± 7.5	11.17 ± 7.5	9.83 ± 3.59	4.6 ± 3.61	
	Mixed breakfast	− 0.83 ± 1.4		6.5 ± 2.17	26.33 ± 3.85	24.17 ± 3.71	17.33 ± 6.29	13.5 ± 4.51	10 ± 3.32	2.6 ± 0.92	
Incremental blood glucose above baseline	Hyperglucidic breakfast	0.22 ± 0.04		0.85 ± 0.19	2.22 ± 0.37	0.77 ± 0.44	0.23 ± 0.25	− 0.22 ± 0.25	− 0.03 ± 0.15	− 0.06 ± 0.26	
	Mixed breakfast	0.07 ± 0.13		0.08 ± 0.12	1.57 ± 0.5	0.33 ± 0.46	− 0.27 ± 0.39	− 0.15 ± 0.34	− 0.15 ± 0.18	− 0.2 ± 0.3	

Values are given as mean ± SEM

lowing these two breakfast tests did not show any significant difference. However, when comparing only values between 0 and 90 min the ANOVA detected higher blood glucose values in the hyperglucidic breakfast test ($p < 0.01$). The area under the blood glucose curve over 180 min was 948.24 ± 24.80 mmol/l × 180 min after the hyperglucidic breakfast vs 900.7253.88 (NS) after the mixed breakfast. The area under the blood glucose curve over 120 min was 667.4 ± 29.03 mmol/l × 120 min after the hyperglucidic breakfast vs 624.2 ± 37.36 (NS) after the mixed breakfast. When incremental blood glucose values above baseline were compared, there was a highly significant difference between the two curves ($p < 0.001$) over 180 min, indicating a higher glucose response in the hyperglucidic test. The Newmans-Keuls procedure allowed a more precise location of the significant difference between 60 and 90 min ($p < 0.01$). There was a non-significant tendency to a higher integrated plasma glucose concentration above baseline after the hyperglucidic test (89.1 ± 26.27 mmol/l × 180 min vs 36.32 ± 33.21, NS). Similarly the incremental plasma glucose value during the first 120 min of the test was not different although a non-significant tendency can be described (80.93 ± 31.24 vs 15.62 ± 50.22). The area under the insulinaemia curve over 180 min was 4675.2 ± 1418.86 mmol/l × 180 min after the hyperglucidic breakfast vs 3943.4 ± 425.35 (NS) after the mixed breakfast. The area under the insulinaemia curve over 120 min was 667.4 ± 29.03 mmol/l × 120 min after the hyperglucidic breakfast vs 624.2 ± 37.36 (NS) after the mixed breakfast. Incremental insulin responses were not statistically different, although there was a non-significant tendency to a higher integrated insulin concentration above baseline after the hyperglucidic test (3178.3 ± 1386.72 × 180 min vs 2143.4 ± 136.68 μU/ml, NS). Similarly the incremental insulin value during the first 120 min of the test was not different (2898.58 ± 953.15 vs 1868.37 ± 551.53).

Calculations were made to compare the insulinogenic effect of increments in blood glucose levels after both tests. The ratio of the maximal insulin increment on the maximal blood glucose increment did not statistically differ (21.02 ± 4.38 μU/mmol × 10^3 for the hyperglucidic breakfast vs 30.12 ± 11.34 for the mixed breakfast), neither did the ratio of the maximal insulin value on the maximal glucose value (7.93 ± 2.065 μU/mmol × 10^3 for the hyperglucidic breakfast vs 6.55 ± 0.81 for the mixed breakfast).

Discussion

The standardized breakfast test which has been used in this study is derived from the test developed by Lefèbvre and Luyckx [12]. We introduced some modifications in meal composition in order to fit with average French habits. In particular, the usual French breakfast is less equilibrated and mostly composed of carbohydrates [13]. The quantity of carbohydrates (76 g) was chosen in order to obtain a similar increase in blood glucose as during a standard 75 g OGTT. We reported elsewhere that this breakfast tolerance test, in obese subjects, induces the same increase in blood glucose as OGTT [14].

The main finding of this study is that, with this 'hyperglucidic' breakfast test, our 38 subjects investigated for PRH exhibit 47.3 % lower blood glucose values than 3.3 mmol/l. This frequency is similar to the results obtained by Palardy et al. [7] who, using ambulatory glycaemic autocontrol reported blood glucose levels lower than 3.3 mmol/l during symptoms 28 patients. Thus, it seems likely that this breakfast test detects a tendency to low blood glucose values, in such patients, with the same frequency as ambulatory blood glucose measurements. By contrast, such low values are extremely rare with this test in control subjects and in subjects with no postprandial symptoms, while in OGTT a poststimulative hypoglycaemia is very usual [3, 5, 15].

However, one could argue that 3.3 mmol/l represents a moderate hypoglycaemia. Several authors have been more restrictive in their definition of hypoglycaemia and give a cut-off value of 2.8 or 2.2 mmol/l [5, 6]. Clearly, our hyperglucidic breakfast test does not induce values of blood glucose lower than 2.8 mmol/l with an increased frequency in patients referred for signs of hypoglycaemia. This cut-off value at 2.8 mmol/l has been proposed in order to avoid the overdiagnosis of PRH which occurs frequently [1–3]. However, there is a large body of evidence that plasma glucose values between 3.3 and 2.8 mmol/l can induce symptoms of hypoglycaemia. Blood glucose values between 3.6 and 2.6 mmol/l are associated with a detectable impairment in cognitive functions [16] and in some complex performances such as driving a car [17]. The threshold for symptoms of hypoglycaemia is generally close to 3.3 mmol/l: 3.6 mmol/l [18]; 3.4 mmol/l [19]; 3.3 mmol/l [9]; 3.3 mmol/l [7]. On arterialized blood [20] there seems to be a 'hierarchy' of thresholds: 3.9 mmol/l counterregulation; 3.3 mmol/l sympathetic response; 2.8 mmol/l neuroglucopenic symptoms. When blood glucose is maintained at fixed values by the glucose clamp technique, hypoglycaemic thresholds for autonomic and neuroglycopenic signs in healthy individuals are between 4.5 and 3 mmol/l in arterialized blood [21]. It should be pointed out that in this paper we did not measure blood glucose levels on arterialized blood, as was generally done in the studies mentioned above [21–22]. Our goal was to propose a practical, simple test, and the use of arterialized blood would not facilitate its applica-

tion. Thus, we chose to evaluate blood glucose levels on venous plasma, under routine endocrine test conditions. Values of 3.3 mmol/l in venous plasma may correspond to values above 4 mmol/l in arterialized blood; i.e. they remain within the zone where the hypoglycaemic thresholds are usually found. Furthermore, orthostatic position rather than recumbency [22], as well as the particular psychology of this kind of patient [6] may amplify the symptoms. In a recent review on this subject, PJ Lefebvre writes: "*at plasma glucose values around 3.2 mmol/l, palpitations, tremour and sweating may be slightly uncomfortable*" [23]. Thus, although the values of hypoglycaemia in our test do not generally reach the classic cut-off value of 2.8 mmol/l, we think that their occurrence subjects referred for PRH, given that that they very rarely occur in control subjects and that they are able to induce symptoms, are suggestive for the diagnosis of moderate, reactive hypoglycaemic events.

The low frequency of hypoglycaemic symptoms during the chemical hypoglycaemias in our breakfast test deserve comment. The consensus statements [3, 23] insist on the need to clearly demonstrate the simultaneous occurrence of symptoms and low blood glucose values for diagnosing PRH. Clearly, this is a fundamental point when using the OGTT or glycaemic ambulatory control for this purpose, since the OGTT gives too many false- positive results and glycaemic control aims at observing the spontaneous event itself. However, it is not surprising to find a lower frequency of symptoms during our breakfast test. The conditions of this test are not exactly the conditions of the spontaneous PRH. Composition of the hyperglucidic breakfast is standardized, and in some PRH patients the meals could be less balanced, thus inducing a stronger hypoglycaemia with more pronounced symptoms. In addition, the sympathetic response could be reduced by resting and recumbency, as discussed above. Thus, we think that the novelty of this breakfast test is rather to expose a chemical hypoglycaemia (an otherwise very rare event) during the test, than to totally mimic the spontaneous hypoglycaemia with all its symptoms.

Almost half of our group of 38 subjects (group B) referred with PRH have a blood glucose nadir lower than 3.3 mmol/l and thus are likely to also present low blood glucose values after meals in their everyday life. In this study, home monitoring of blood glucose levels with a glucose analyser was not systematically done, but in three of these subjects it showed low blood glucose levels (< 2.8 mmol/l). Probably, most of our subjects with a low glycaemic nadir after the breakfast test are such *bona fide* hypoglycaemic patients. The complex postprandial coordination of a decrease in insulinaemia and an increase in counterregulatory hormones 2–3 h after a meal has been shown to be occasionally deficient. The more classic mechanism is postprandial hyperinsulinism, demonstrated many years ago by Luyckx and Lefèbvre [15]. Obviously, an increased insulin response is the explanation for the excessive decrease in blood glucose in several of our patients. However, in this series, the comparison of insulin responses does not show a marked difference, suggesting hyperinsulinism is not the most important mechanism in this sample. More recently, increased insulin sensitivity has also been found in such patients with the glucose clamp [24] and the minimal model [25]. An increased non-oxidative glucose metabolism has been shown to be involved in this process [26]. Interestingly, when calculating a simple insulin sensitivity index in our patients with the homeostasis model assessment, we also found that this sensitivity was enhanced in patients with PRH. A parallel reduction in the beta-cell function index provided by this model may indicate that during fasting there is a compensatory decrease in insulin release, consistent with the concept of a feedback loop between insulin sensitivity and insulin release [27]. Increased insulin sensitivity is possibly a frequent cause of PRH [25, 26]. A third mechanism, which remains poorly understood, is the possible involvement of moderate defects in glucose counterregulation [23]. For instance, a lowered glucagon response [28] has been reported, although this has not been investigated here. Probably, *bona fide* hypoglycaemia is an heterogeneous condition in which one or several of these abnormalities may be found. The hyperglucidic breakfast test may be a simple tool to assess this multifactorial condition, under physiological conditions. However, more than 50 % of the patients selected on the basis of signs of PRH do not show this abnormal blood glucose nadir lower than 3.3 mmol/l. Many of these subjects are probably "non-hypoglycaemic" patients, i.e. suffering from sympathetic signs after a meal without any postprandial blood glucose decrease [1, 3, 23]. However, some "false negative" responses cannot be excluded, i.e. subjects who undergo hypoglycaemia during their everyday life and do not show this low nadir after the hyperglucidic breakfast.

Another question is why this breakfast detected a particular glycaemic pattern in patients with suspected PRH, while breakfasts administered by other authors [4, 8, 9] did not. Composition of the diverse breakfast tests employed in the literature markedly differs. Compared to the breakfast tests of previous investigators our test is more hyperglucidic. It contains 64 % carbohydrates, while those of Lefebvre and Luyckx [12], Hogan et al. [9] and Charles et al. [4], respectively, contain 47, 50 and 48.3 % carbohydrates. The paper of Buss et al. [8] does not give the exact composition of the breakfast test. By contrast our breakfast test contains less protein than the breakfast test of previous authors (9 vs 15 % for Lefebvre and Luyckx [12] and Hogan et al. [9] and 21.7 % for Charles et al. [4]). Compared to OGTT

our breakfast test is markedly more insulinogenic [14], consistent with other authors who have also reported higher insulin responses in breakfast tests compared to OGTT [29]. However, Buss et al. [8] and Hogan et al. [9] showed similar insulin responses between breakfast and OGTT, and Charles et al. [4] a markedly lower response. In this study, we compared our hyperglucidic breakfast with a more classic mixed breakfast which has been designed to be similar to those of Charles et al. [4] and Hogan et al. [9]. This breakfast induces a higher increase in blood glucose, with no significant differences in insulin response. Thus, this hyperglucidic breakfast test seems to represent a higher glucose stimulus than the mixed meal. This fact is probably not explained by differences in the quantity of carbohydrates, since it has been demonstrated [30] that varying amounts of glucose between 25 and 100 g during an OGTT do not change the amplitude of blood glucose increase. Thus, the overall composition of the breakfast test is probably responsible for this higher hyperglycaemic effect. Such a difference in blood glucose response probably explains some of the discrepancies between our results and the negative results of previous investigators. Presumably, they employed meals which were too balanced to reproduce the conditions which lead to hypoglycaemia in this category of patients.

In conclusion, 47 % of subjects in whom PRH was suspected had a blood glucose level lower than 3.3 mmol during this breakfast test, i.e. values which could induce hypoglycaemic symptoms and neurological impairment. The occurrence of false positive responses which would be artefacts of the breakfast test (as occurs during OGTT) does not seem likely since subjects other than those assessed for suspicion of PRH had very few (1 to 2 %) low blood glucose levels after this test. Moreover, this test is fully physiological and mimics current nutritional habits, so that subjects who undergo hypoglycaemia during the test may also experience hypoglycaemia during their everyday life. However, this hyperglucidic breakfast possibly induced some false negative responses, i.e. several subjects with true PRH during their everyday life may fail to show a blood glucose value lower than 3.3 mmol during this test. Nevertheless, we think that hyperglucidic physiological breakfasts such as the one presented here, fitting with normal nutritional habits, are a good alternative to ambulatory glycaemic testing for the diagnosing of PRH, and are easier to perform.

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