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Clinical Case

Oral Glucose Tolerance Test by Pure Glucose Vs. Sucrose to Diagnose a ‘‘Mild’’ Early Reactive Hypoglycemia. A Case Report

L’hyperglycémie provoquée par voie orale au glucose pur vs au saccharose pour diagnostiquer une hypoglycémie réactionnelle précoce ‘fruste’ : à propos d’un cas

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ABSTRACT

We report the results of glycemic indexes and several oral glucose tolerance test with pure glucose ($OGTT_{Glc}$) *vs.* sucrose ($OGTT_{Sucr}$). In October 2021, all of the patient's blood glucose levels were normal. During $OGTT_{Glc}$: $T1H_{Glc} < T0_{Glc}$ or during $OGTT_{Sucr}$: $T1H_{Sucr} > T0_{Sucr}$. In January 2022, blood glucose levels were still normal, Insulin resistance was occurring (HOMA-IRoct = 2.20 vs HOMA-IRjan = 3.68) and Insulin sensitivity was gradually collapsed. This allowed us to diagnose a 'mild' early reactive hypoglycemia. OGTT remains the best means for a clinical exploration of glucose metabolism disorders.

RÉSUMÉ

Nous rapportons les résultats d’indices glycémiques et de plusieurs hyperglycémies provoquées par voie orale au glucose pur ($HGPO_{glc}$) et saccharose ($HGPO_{Sacc}$). En octobre 2021, toutes les glycémies de la patiente étaient normales. Pendant l’$HGPO_{glc}$: $T1H_{Glc} < T0_{Glc}$ or durant l’$HGPO_{Sacc}$: $T1H_{Sacc} > T0_{Sacc}$. En janvier 2022, les glycémies étaient toujours normales, l’insulinorésistance apparaissait ($HOMA\text{-}IR_{oct}$ = 2,20 *vs* $HOMA\text{-}IR_{jan}$ = 3,68) et l’insulinosensibilité s’effondrait progressivement. Ceci nous a permis de poser le diagnostic d’hypoglycémie réactionnelle précoce ‘fruste’. L’HGPO demeure l’examen de choix pour l’exploration clinique des troubles du métabolisme du glucose.

INTRODUCTION

Nowadays, hypoglycemias in adulthood are defined as the Whipple triad combining 1* fasting hypoglycemia, 2* relevant neuroglycopenic (NGP) symptoms and 3* disappearance with sugar [1]. When some components of this triad are missing, it defines Reactive Hypoglycemia (RH) that causes neuro-vegetative discomforts in postprandial situations. However, many researchers still doubt its existence [2;3;4]. Moreover, the classification of RH is still in debate, but it can be subdivided into three classes (Table 1) [5; 6]. Its challenging to diagnose, because based on questioning and different diagnostic approaches, i.e. Oral Glucose Tolerance Test with pure glucose ($OGTT_{Glc}$), OGTT with sucrose ($OGTT_{Sucr}$), Mixed meal, long fast, etc. [4;5;6]. While a part of researchers postulate that using OGTT would be the best means to diagnose it [3], others believe that an OGTT should never be used for the evaluation of suspected postprandial hypoglycemia [2]. Besides, the RH diagnostic thresholds are not agreed. The majority of patients checked for NGP symptoms do not show any classic hypoglycemia (i.e. < 3.3 mmol/L) [3]. The present case report illustrates this situation and allows us to analyze the results of glycemic indexes and $OGTT_{Glc}$ *vs.* $OGTT_{Sucr}$ to diagnose an Early Reactive Hypoglycemia (ERH) with normal glycaemia values.

CASE PRESENTATION

In March 2021, a 47 years old woman, was seen in consultation as part of the annual medical examinations. She reported a medical concern about an unexplained primary infertility for which she underwent in vitro fertilization. This has allowed her to have only one child to date. She also reported a high blood pressure, which is balanced with indapamide 1.5 mg: 1t/d. At that time, her clinical parameters were normal (body mass index ‘BMI’: 21). Neither alcohol nor tobacco consumption was mentioned. However, the prescribed paraclinical assessment revealed an Impaired Glucose Tolerance

(IGT) and/or Impaired Fasting Glucose (IFG) (i.e. fasting blood glucose: 6.59 mmol/L (normal ranges: 3.6 – 6.1 mmol/L). Given this result, the patient was referred to the Endocrinology-Metabolism Service of the Libreville University Hospital for the appropriate care.

In April 2021, during her Endocrinology visit, she mentioned her avoidance of "sugary" foods for several years and reported episodes of lipothymia after sugar-rich meals. During this visit, she was prescribed a regular physical activity (fast walking 3 times a week; at least 30 minutes each session), and a fractionated (5 meals/d) low-carbohydrate diet (50% carbohydrates i.e. approximately 180g/d). It was then scheduled a trimestrial follow-up visit.

In July 2021, BMI: 20.8. The patient's assessment showed her level of glycated hemoglobin to be normal, i.e. 5.43%

In October 2021, BMI: 20.4. A more detailed investigation of the patient's glucose metabolism was carried out on October, 21st 2021 by Laboratories Service of the Mother and Child University Hospital-Foundation Jeanne Ebori. This investigation consisted of:

1. 3 steps OGTT (T0-T1H-T2H of 75g pure anhydrous glucose dissolved into 300 ml of spring water then ingested within 5 minutes). The glucose levels were determined within 1 hour of the final samples using the optical glucose oxidase method on the Cobas c111 according to the manufacturer's instructions (Roche Diagnostic, Germany).
2. Insulin and C-peptide measurement: Dosage were done within one hour following the blood sampling using Cobas e411 and applying the manufacturer's instruction. (Roche Diagnostic, Germany).
3. Glycemic indexes determination: HOMA (Homeostatic Model-Assessed) -IR (Insulin Resistance); -β (Insulin sensitivity); QUICKI (Quantitative Insulin Sensitivity Check Index), and DIo (Oral disposition index) were calculated with following formulas.

$$\text{HOMA-}\beta = 20 * \frac{insulin\ T0}{[0.055 * Glucose\ T0] - 3.5} \qquad \text{HOMA-IR} = \frac{insulin\ T0 * glucose\ T0}{22.5}$$

$$\text{QUICKI} = \frac{1}{[\log insulin\ T0 + \log Glucose£\ T0]} \qquad \text{DIo} = \frac{\Delta Insulin0-1H}{\Delta Glucose£0-1H} * \frac{1}{Insulin\ T0}$$

£ *Glucose in mg/dl.*

Our findings

The patient's $OGTT_{Glc}$-T0 was normal; Glucose levels at T1H-75 g of pure glucose were lower than fasting glucose levels during two (2) different $OGTT_{Glc}$ 1 week apart (on October, 21st and 28th 2021): $T1H_{Glc}$ (4.36 ± 0.10 mmol/L) □ $T0_{Glc}$ (4.87 ± 0.10 mmol/L) (Fig.1);

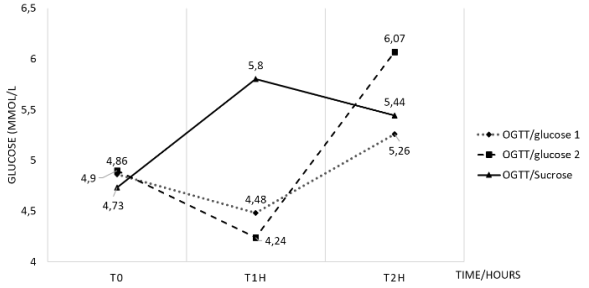

Fig.1: Data for the various OGTT pure glucose vs. sucrose

Fastings C-peptide (2.09 ng/mL) and insulin (10.17 IU/mL) levels were also within normal ranges (Table 2); The glycemic indexes revealed no insulin resistance (IR), HOMA-IR = 2.20; but a slight collapsed insulin sensitivity (IS) (HOMA-β: 0.15; DIo_{1h}: - 1.15). Indeed, the QUICKI index was not impaired (0.339) (Table 2).

These unusual results pointed to a 'mild ERH' (name chosen because ALL glucose rates are in normal ranges and are not so low considering the classical definition of RH (i.e. ≤ 3.3 mmol/L)). We decided to perform, one week apart, an OGTT with sucrose to confirm it [4; 9].

In November 2021, BMI: 22.76. The $OGTT_{Sucr}$ was performed on November, 4th 2021 and showed an inversion of the curve with a blood glucose level at 1 hour higher than fasting blood glucose level: $T1H_{Sucr}$ (5.8 mmol/L) □ $T0_{Sucr}$ (4.73 mmol/L) (Fig.1). Normal Cortisol rate: 308.38 nmol/L (138 – 690 nmol/L). Normal TSH rate: 1.14 µUI/ml (0.27 – 4.2 µUI/ml). Then, in the absence of Alpha Glucosidase Inhibitors (AGI), not available in Gabon, the patient was treated with Repaglinide 0.5 mg (1 t/d before the main meal).

In January 2022, BMI: 24.40. The patient was re-evaluated. Biologically, the findings (Table 2) were: IR appear: fasting insulin (16.69 µUI/mL); $HOMA\text{-}IR_{janv}$ = 3.68; and IS progressively collapsed. All three (3) calculated indexes were now disturbed ($HOMA\text{-}\beta_{Jan}$: 0.22; $DIo_{1H\text{-}Jan}$: - 2.54; and $QUICKI_{Jan}$: 0.315) (Table 2).

DISCUSSION

By convention, RH diagnostic is established when plasma glucose rate goes below 3.0 mmol/L after a meal or during an OGTT [5; 6]. In this case report, all of the patient's blood glucose rate were normal. During $OGTT_{Glc}$, the 1-hour glucose rate was lower than the fasting blood sugar rate. This finding was confirmed by another $OGTT_{Glc}$ performed a week later (Fig. 1). However, this surprising result was expected for minor clinical NGP signs present by the patient after meals and the weak nature of our results. Moreover, it indicated that $OGTT_{Sucr}$ should be performed to diagnose a "mild" RH, i.e. an RH with normal blood glucose rates [4;6]. $OGTT_{Sucr}$ allowed us to observe that the T1H-glucose rate was higher than T0-glucose rate (Fig. 1) and then to confirm the diagnosis. Faced of these atypical findings, the Clinical Practice Guideline of Endocrine Society recommends to formally recreate the circumstances in which symptomatic hypoglycemia are likely to occur in order to confirm the diagnosis of RH by demonstrating a glucose level below 3.0 mmol/L [2]. Unfortunately, the quality of the technical

facilities in Gabon did not allow us to perform more precise analysis (i.e. insulin auto-antibodies determinations) apart from the cortisol (8 AM) and TSH determinations, which were otherwise normal. Let's remember that hypoglycemia due to the development of insulin antibodies usually occurs in fasting state and is a rare disorder reported to occur primarily among people of Japanese or Korean ethnicity [2;5;7]. In the present case report the results allow us to diagnose a "mild" Early Reactive Hypoglycemia (ERH). Indeed, RH, utterly different from the fasting ones, can be subdivided into three classes (Table 1) in which Alimentary RH is the more frequent class. Addressing Alimentary RH is symptomatic and consists of modifying the dietary habits by fractioning meals, reducing nutrients with high glycemic indexes and reducing alcohol [5; 7]. In case of failure, it is recommended that the patient get an AGI (i.e. acarbose or miglitol) that will slow the glucose molecule bioavailability within the intestinal light and reduce their absorption [9]. Ahmadpour S et al. revealed that Idiopathic RH, an alimentary RH, was more frequent among women and lean persons [10]. A Scandinavian study did not confirm this assertion [3]. It should be pointed out that our case was a mature woman with a normal but trending downwards BMI. It cannot be overemphasized that in any patient with hypoglycemia, treatment with medication must be considered as recommended by the Clinical Practice Guideline of Endocrine Society [2]. AGI and Metformin therapy may be recommended in late RH with IFG [9]. Also, Metformin, AGİ, Thiazolidinediones (TZD), or Incretins and Analogous of Glucagon-like peptide-1 Receptor may be recommended if there is late RH with IGT [9]. Unfortunately, AGI and TZD are not available in Gabon. We did not prescribe Metformin either because the patient had a trending downwards BMI. In addition, the known side effects of Metformin could have increased weight loss in her case. Finally, the patient was treated with Repaglinide, an insulin secretagogous, instead of Metformin.

In this case report, despite a good insulin production, the results show that IR, not detected in October (normal insulin level and HOMA-IR_{oct} = 2.20), appears three months later (increased fasting insulin: 16.69 µUI/mL in January 2022 *vs.* 10.17 µUI/mL in October 2021; HOMA-IR_{jan} = 3.68) (Table 2). According to Altuntas Y et al., the threshold of fasting insulin level for IR was accepted as 13 µU/ml [11]. Indeed, the increasing insulin level may be due to the treatment with an insulin secretagogous, but without impacting blood glucose levels.

Regarding calculated glycemic indexes, the HOMA-IR index illustrates IR before diabetes appears and offer sanitary and dietary measures to the patient, it can also recommend treatment to lower IR [12]. Concerning QUICKI index, a low rate indicates a decrease in IS [16]. Ideally it should be above 0.33 as we find in October ($QUICKI_{Oct}$ = 0.339). Finally, the Oral Disposition Index (DIo) is a good indicator of β-pancreatic cell function [13]. Indeed, the negative predictive value (high probability of not developing diabetes) is valid for a DIo ≥ 1.24 [13]. The DIo can be useful to help identify subjects who are at increased risk of developing diabetes [13]. It is well admitted that the two common disorders frequently associated with IR are PCOS and type 2 diabetes, which affect respectively 4-6% and 2-6% of women in the reproductive age [11]. People with IR (i.e. IFG and/or IGT) are prone to develop Type 2 Diabetes in the future. Indeed, the annual incidence of diabetes among people with various categories of IFG (i.e. fasting glucose ≥ 6.1 mmol/L) or IGT (i.e. fasting glucose < 7.0 mmol/L or OGTT-T2H ≥ 7.8 mmol/L and < 11.1 mmol/L) varies from 5 to 10% [14]. In a meta-analysis, Gerstein HC, et al. estimated the risk of progression of diabetes [14]. They report that compared to normoglycemic people, the relative risk (RR) for diabetes was: 5.52 in people with isolated IGT; 7.54 in people with isolated IFG and12.13 in people with both IFG and IGT [14]. However, our case report initially presented an IFG and/or IGT and a subsequently IR. Indeed, at the beginning, our patient presented a fasting glucose of 6.59 mmol/L, rapidly balanced (HbA1c: 5.43%) with physical activity and a fractionated diet. The results of $OGTT_{Glc}$ and $OGTT_{Sucr}$ allowed us to diagnose an ERH named 'MILD' because, taken together, ALL glucose rates during the three OGTT were in normal ranges and not so low considering the classical definition of RH (i.e. ≤ 3.3 mmol/L)).

After 2 months on Repaglinide, in clinical point of view, we can say that treatment had a beneficial effect on the patient. Indeed, she did not report any episode of lipothymia, or discomfort after meal. In some extent, we can unfortunately say that treatment with Repaglinide have no benefit on our patient's glycemic indexes. The latter show an increasing IR and a time-collapsed IS. Knowing that hypoglycemic disorders are rare in persons without diabetes, recommendations for their evaluation and management must rely largely on clinical experience [2].

CONCLUSION

Taking into account the increasing fasting insulin value from 10.17 µIU/mL to 16.69 µIU/mL in trois months, it becomes urgent to change her medical prescription by a low dose insulin-sensitizer (i.e. Metformin: 280 mg/d). Although, use of the OGTT may be consider as a suboptimal method for the initial diagnosis of RH, it does demonstrate IS and provides a better diagnostic approach to RH. **Patients with RH, even if they are lean or with normal weight, should be considered at risk of diabetes in the future** [15; 18]. The investigation of this clinical case confirms the usefulness of **OGTT** in relation to glucose metabolism disorders in general and **RH** specifically.

DECLARATIONS

Informed consent

The patient provided us with her informed and signed consent before participating in the study. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, and with the approval of the CHUME-FJE Scientific Committee.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author contributions

EL, DN and M-ANepM-M conceived and designed the study. LM, ML, LN and AA contributed to sample collection and dosages. EL, EBN and JFDS prepared the first and subsequent drafts of this manuscript to which all authors contributed. All authors reviewed and approved submission of the final manuscript.

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Data availability statement

Not applicable.

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Fig.1: Data for the various OGTT pure glucose *vs.* sucrose

Table 1: Post-prandially Reactive Hypoglycemia Classes and Sub-groups [5; 6]

Sub-groups	Onset time during OGTT or after meals	Mechanisms involved
Alimentary Reactive Hypoglycemia		
Early Reactive Hypoglycemia (ERH)	in the first 1-2 hours of OGTT	May be due to accelerated gastric emptying, or exaggerated incretin effect.
Post-gastric surgery Hypoglycemia (i.e. Roux-en-Y bypass)	within 2 to 3 hours after a meal	May be due to increased insulin secretion in response to rapid and unregulated nutrient absorption or alterations in the secretion of gut hormones modulating insulin release in response to food.
Idiopathic Reactive Hypoglycemia (IRH)	at the 3rd hour of OGTT	The cause and pathophysiological importance have not been fully elucidated. It occurs mostly in teenagers and nonobese. This type of hypoglycemia usually does not develop diabetes. GLP-1[#] may be involved in the pathogenesis
Hormonal Reactive Hypoglycemia		
Late Post-prandially Reactive Hypoglycemia	at the 3rd-5th hour of OGTT	May be partially due to insulin resistance syndrome. It is probably a cause of delayed insulin secretion
Diabetic Reactive Hypoglycemia		
Early Type 2 Diabetes Mellitus	late (4 to 5 hours) after meals	Hypoglycemia is due to an excessive and delayed insulin release, which occurs at the time their blood glucose falls. In these patients, the postprandial hypoglycemia disappears with the progression of the diabetes and the development of a more significant degree of peripheral insulin resistance.

[#] GLP-1: Glucagon-like peptide-1

Table 2: A 3 months variation for patient's glucidic parameters

Glucidic biomarkers and indexes	Measured values (patient)		Threshold
	October 2021	January 2022	
Fasting C-peptide (ng/mL)	2.09	--	0.010 – 40.0
Fasting insulin (µUI/mL)	10.17	16.69	3 – 13
Fasting glucose (mmol/L)	4.87	4.97	≥ 3.6 - < 6.1
HOMA-IR	2.20	3.68	0.7 – 2.20
HOMA-β	0.15	0.22	0.7 – 2.20
QUICKI	0.339	0.315	□ 0.33
DIo (1h)	-1.15	-2.54	≥□1.24