Pathologie Biologie 64 (2016) 49–52

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

Biological diagnosis of diabetes mellitus

Diagnostic biologique du diabète sucré

M. Zendjabil

Laboratoire de biochimie, Établissement Hospitalier Universitaire d'Oran 1er Novembre 1954, BP No. 4166, Ibn Rochd, Oran, Algeria

ARTICLE INFO

Article history:
Received 23 July 2015
Accepted 7 October 2015
Available online 6 November 2015

Keywords:
Diabetes mellitus
Diagnosis
OGTT
HbA_{1c}

Mots clés :
Diabète sucré
Diagnostic
HGPO
HbA_{1c}

ABSTRACT

Diabetes mellitus is a common disease whose complications are severe. For decades, the diagnosis of diabetes and prediabetes was using only fasting glucose or glucose two hours during an oral glucose tolerance test. Recently, it is possible to use HbA_{1c}. Each of these tests has advantages and limitations that must be well known by clinicians for better care for patients. So they could use one, two or three of this tests to reach to a proper diagnosis. The aim of this article is about the strong and weak points of these tests.

RÉSUMÉ

Le diabète sucré est une maladie fréquente dont les complications sont graves. Pendant des décennies, le diagnostic du diabète et du prédiabète faisait uniquement appel à la glycémie à jeun ou la glycémie deux heures après une épreuve de glycémie provoquée par voie orale. Depuis peu, il est possible d'utiliser l'HbA_{1c}. Chacun de ces tests a des avantages et des limites qui doivent être bien connus par les cliniciens pour une meilleure prise en charge des patients. Donc, ils pourraient utiliser un, deux ou trois de ces tests pour arriver à un bon diagnostic. Le but de cet article est de traiter les points forts et les inconvénients de ces tests.

1. Introduction

Diabetes mellitus is a very common disease with deadly complications. The number of diabetics patients in 2013 was 382 million and it is expected to increase to reach 592 million in 2035 [1]. Diabetes mellitus often goes unnoticed and the average lag between onset and diagnosis is 7 years [2]. In the United States of America, approximately 30% of diabetics or 6,2 million people are underdiagnosed [3]. The definition of diabetes is mainly biological view and has changed throughout the years, especially with the recent introduction of HbA_{1c}. The aim of this article is about the strong and weak points of the tests used to diagnose this disease.

2. Fasting plasma glucose (FPG)

Diabetes mellitus is defined according to American Diabetes Association (ADA) and World Health Organization (WHO) by a concentration of FPG higher than 126 mg/dl twice or a blood glucose above 200 mg/dl at any time of day [4,5]. The threshold of 126 mg/dl was chosen because it is from this level that the risk of microvascular complications, including diabetic retinopathy, becomes important. Three epidemiological studies have contributed to establish this threshold. However, these studies had a strong bias: research retinopathy was made in an incomplete and imprecise manner. New research has shown that the threshold value of 126 mg/dl had a sensitivity of less than 40% and a specificity of between 81 and 96% for the detection of diabetic retinopathy. So there appears to be no threshold value for evaluating the presence of this complication [6].

Glucose can be measured in serum, plasma or blood. Plasma values are 11–13% higher than the measured blood glucose in the case of a normal hematocrit, this is due to the difference of the amount of water between erythrocytes and plasma [7]. The glucose assay must be done in laboratory. Point of care tests (POCT) glucometers are very useful for monitoring diabetes mellitus, but should not be used for the diagnosis due to both insufficient precision and accuracy and the inherent, sample-dependent flaw

E-mail address: z-mustapha2@hotmail.fr

http://dx.doi.org/10.1016/j.patbio.2015.10.002
0369-8114/

of results [8]. However, some authors suggest otherwise, arguing that POCT instruments have sufficient accuracy to be used as diagnostic tools for diabetes [9].

3. Oral glucose tolerance test (OGTT)

This is the most known dynamic test in diabetology, which has been widely used. This test is to administer in less than 5 mins, 250 ml of water with a glucose load of 75 g for adults and 1.75 g/kg body weight for children. Then, blood glucose dosage is carried out at different times. Standardization was established for reducing the importance of variation coefficients for different glucose concentrations determined during the test. Thus, we should take into consideration only the FPG and blood glucose 2 h after an OGTT (2-h PG) [10] and it is no longer necessary to extend this test to 3 or 5 h. If positive, it is necessary to repeat the test to confirm the result; this is not always respected in practice because of various constraints imposed by the test. Depending on the value of 2-h PG after the load, patients are classified into normal subjects for levels below 140 mg/dl, subjects with impaired glucose tolerance (IGT) when values are between 140–199 mg/dl and diabetics when blood glucose exceeds 200 mg/dl.

This test was first described in 1922 and was designed to assess the ability to tolerate a glucose load. It was only in 1979 that the National Diabetes Data Group has recommended its use for the diagnosis of diabetes mellitus, followed by the WHO a few years later. In 1997, a group of experts recommend not to use this test primarily for the diagnosis of diabetes [11]. The ADA had probably the wish that this test becomes obsolete because it has a low reproducibility; it is expensive, long and mobilizes the staff for significant period. By issuing these recommendations, the ADA hoped to attract more patients to be screened, diagnosed and treated with simple measurement of FPG.

The OGTT is indicated when the FPG value is between 110–126 mg/dl without a metabolic syndrome, if the FPG is normal in presence of glycosuria or when FPG is normal while the PPG is between 140–200 mg/dl. However, OGTT should not be used in certain situations: when FPG and lipid levels are normal, if the patient's age is above 70 years because the result does not influence the therapeutic management. It was also demonstrated that the OGTT was not of interest when FPG level is greater than 126 mg/dl, because this value is equivalent to 2-h PG higher than 200 mg/dl, in the risk of development of diabetic retinopathy [12].

Although the OGTT is decried in favor of FPG, it has been widely used in clinical and epidemiological research studies and it is still considered as "the gold standard". It also keeps an important place in clinical practice, in particular for the early detection of IGT for which it has better sensitivity than FPG. Determining parameters other than glucose such as insulin and C-peptide during the test allows for calculation of indices reflecting insulin secretion and insulin resistance are used in the field of research [13]. In a study including 406 subjects with prediabetes, many indices were studied and it was found that high levels of glucose and a low concentration of C-peptide at 30 mins after OGTT may be a good predicator for diabetes conversion [14].

The OGTT is particularly useful in the diagnosis of gestational diabetes (GD) that may be accompanied by some perinatal complications. Thus, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study which included over 25,000 women showed a continuum between blood glucose levels in pregnant women and the risk of perinatal complications such as fetal hyperinsulinemia, macrosomia, neonatal hypoglycemia and cesarean [15]. The use of OGTT to search for GD was the subject of many controversies including the best time to conduct the test, the glucose load to administer 75 or 100 g, and the thresholds to be considered as pathological. Due to an international consensus of International Association of Diabetes in Pregnancy Study Group (IADPSG) [16], responses have been made to these questions. Thus, the OGTT should be performed between 24 and 28 weeks of gestation with a glucose load of 75 g. The thresholds of blood glucose values are 92 mg/dl for the FPG, 180 mg/dl after 1 h and 153 mg/dl after 2 h [17,18]. These recommendations tend to increase GD's prevalence [19] (from 5–10% to 15–20%). In two randomized controlled trials, 80 to 90% of women with mild GD diagnosed by this strategy could be managed with life-style therapy only. Other well-designed clinical studies are required to determine the best way to detect and treat women with GD, diagnosed according to the IADPSG recommendations [20].

The determination of postprandial blood glucose (PPG) involves measuring blood glucose 1 h or 2 h after a meal. Normal values of PPG are less than 140 mg/dl. The value of PPG depends on many factors such as the nature of the meal, various gastrointestinal and pancreatic hormones, or the rate at which gastric emptying is carried out. PPG appears to be an independent minor cardiovascular risk factor, but when it is combined with other risk factors such as high cholesterol, high blood pressure or smoking; the risk is significantly increased; which could explain the high prevalence of cardiovascular morbidity and mortality in diabetic patients, particularly in type 2 diabetes [21]. The multicenter European study DECODE showed that the risk of cardiovascular morbidity and mortality is more correlated with postprandial hyperglycemia during an OGTT than FPG [22]. The PPG has been recognized as an independent cardiovascular risk factor in several other meta-analyzes [23,24], but the relationship between GPP and microvascular risk remains to our knowledge little studied. Further studies report a reduction in cardiovascular events in patients treated with drugs reducing PPG like acarbose [25,26]. Postprandial hyperglycemia is therefore an interesting therapeutic target, particularly when the HbA_{1c} is close to the aim.

4. Glycohemoglobin HbA_{1c}

HbA_{1c} is defined by the slow and irreversible binding of glucose to the N-terminal valine of one or both of the beta chains of hemoglobin. It reflects glycemic control of two or three months [27]. HbA_{1c} was discovered in the 1960s. The first demonstration of this marker increase in diabetes was made by Trivelli et al. in 1971 [28]. In 1986, the NGSP (National Glycohemoglobin Standardization Program) has established a reference method using HPLC (High Performance Liquid Chromatography) based on the DCCT (Diabetes Control and Complications Trial) and UKPDS (United Kingdom Prospective Diabetes Study) studies that showed a significant correlation between HbA_{1c} and the risk of occurrence of complications in diabetic patients [29]. The IFCC has proposed in 2002 a reference technique using HPLC coupled with capillary electrophoresis (HPLC-CE) or mass spectrometry (HPLC-MS) and has defined the N-terminal hexapeptide of the standard to use [30]. Several consensuses have been established in the late of 2000s that is allowed to standardize the A1 C test [31,32]. It was also decided that the results provided by the laboratories must now be expressed in two units: mmol/mol (IFCC) and % (NGSP), with a master equation linking the two expression systems.

For decades, the diagnosis of diabetes was based only on FPG or 2-h PG after an OGTT. The use of HbA_{1c} as a diagnostic tool was suggested in the 1970s and early 1980s but with an adaptation of the values for pregnant women and elderly [33]. Eventually in 2009, a committee of experts supported by the ADA and EASD (European Association for the Study of Diabetes) proposed HbA_{1c} as a diagnostic marker [34]. This decision was followed by the WHO in 2011 [35]. The chosen criteria are: $HbA_{1c} \geq 48$ mmol/mol