Diabetes Mellitus: Once More About Diagnostics.

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ABSTRACT

Background: Early identification and precise diagnosis of diabetes is crucial. However, determination of diabetes cases leads to psychological, social and economic consequences. Due to this fact, diagnosis of diabetes mellitus should be validated. However, there are some discrepancies in diabetes diagnostics and defining criteria.

Objective: The purpose of this study was to investigate whether the criteria random plasma glucose ≥200 mg/dL (≥11.1 mmol/L) in the presence of the classic hyperglycemic symptoms " is reliable and is there need to change this criterion for diagnosis of diabetes mellitus.

Material and Methods: Specificity of diabetes classic symptoms were investigated by literature analysis for identification of these symptoms' frequency in other diseases and conditions. The data of 134 people were analyzed in this study. Venous plasma glucose researched at fasting and 30, 60, 90, and 120 minutes after a 75.0-g glucose load (Precision PCx Medi Sense, Abbot, USA), as well as A1c levels (SDA1c Care, SD Biosensor, Korea). Statistical analysis was performed by using Fischer exact.

Results Diabetes classic symptoms analysis demonstrated their non specificity. Specificity of random plasma glucose ≥ 250 mg/dl was statistically highly significant ($p < 0.00001$) than random plasma glucose ≥ 200 mg/dl: 100% vs 69%.

Conclusion: In the presence of classic hyperglycemia symptoms it is recommended to diagnose diabetes by using random plasma glucose ≥ 250 mg/dl.

Keywords

Random plasma glucose, diabetes mellitus diagnosis, classic hyperglycemia symptoms.

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Diabetes mellitus (DM) is a widespread disease very often characterized by greater chances of developing severe complications, poor prognosis and significant costs [1]. The disease is still considered incurable, although we are increasingly talking about remission [2,3], and the diagnosis itself has a serious negative impact on the person, family, friends, and others [4].

The criteria for DM diagnostics proposed by various organizations based on [5, 6, 7, 8, 9, 10, 11]:
- fasting glycaemia (FG) ≥126 mg/dL or ≥ 7.0 mmol/L;
- glycaemia 2 hours after a 75-g glucose load (G2h) ≥ 200 mg/dL or ≥ 11.1 mmol/L;
- HbA1c levels (≥ 6.5% or ≥ 48 mmol/mol) are identical.

In guidelines by American Diabetes Association [5], International Diabetes Federation [6], World Health Organization [7], American Association of Clinical Endocrinology [8], Canadian Diabetes Association [9], United Kingdom [10], Australian Diabetes Society [11] there is also a fourth item: the presence of classic hyperglycemic symptoms (or sings of hyperglycemic crisis) jointly with a random plasma glucose (RPG) ≥ 200 mg/dL or ≥ 11.1 mmol/L.

It should be noted that the guidelines by WHO [12, 13], by Diabetes Australia [14] and by Azerbaijan Association of Endocrinology, Diabetology and Therapeutic Education (AAEDTE) [15] do not contain this composite indicator for the diagnosis of DM.

We would like to notify that the document of WHO dated 2019 "World Health Organization Classification of Diabetes Mellitus" [7], indicates that random plasma glucose can be used for patients with classic symptoms of DM. Authors referred to WHO document of 2011 "Use of Glycated Hemoglobin (HbA1c) in the diagnosis of Diabetes Mellitus. Abbreviated Report of a World Health Organization Consultation" in which, however, these recommendations are absent. In addition, authors of WHO 2019 [7], don't clarify whether changes occurred in official position of WHO regarding the diagnostic criteria for DM.

The purpose of this study was to investigate whether the criteria RPG ≥200 mg/dL (≥11.1 mmol/L) in the presence of the classic hyperglycemic symptoms " is reliable and is there need to change this criterion for diagnosis of DM.

Materials and methods
The study consisted of three parts.
The task of the first part was to determine how specific to DM symptoms of hyperglycemia which are considered "classic". In order to answer this question, the frequency of these symptoms in other diseases and conditions was analyzed. The first part of the study involved a review of the literature published in PubMed.

The task of the second part of the study was to analyze the incidence of glycemia levels of 200 mg/dL (11.1 mmol/L) or more in the postprandial state in people with newly diagnosis DM, prediabetes

(PD), and normal glucose metabolism (NGM). The results of the glucose tolerance test were used as a model of the postprandial state.

The task of the third part of the study was to determine the optimal RPG level for the diagnosis of DM in the presence of classic hyperglycemic symptoms.

During the second and third parts of the study, the results of 134 people were analyzed. Six subjects had DM, 41 had PD and 87 had NGM.

The examination determined glucose in venous plasma at fasting and 30, 60, 90, and 120 minutes after a 75.0-g glucose load (Precision PCx Medi Sense, Abbot, USA), as well as A1c levels (SDA1c Care, SD Biosensor, Korea).

Table 1 shows the criteria used to assess the results of the examination.

Table 1: Diagnostic criteria for NGM, DM and PD according to AAEDTE [15].

Parameters	Units	NGM	PD	DM
HbA1c	%	≤ 5.6	5.7-6.4	≥6.5
	mmol/mol	≤38	39-47	≥48
FG	mg/dl	<110	110 - 125	≥126
	mmol/l	<6.1	6.1- 6.9	≥7.0
G2h	mg/dl	≤139	140 - 199	≥200
	mmol/l	≤7.7	7.8 – 11.0	≥11.1

Statistical analysis was performed by the Fisher exact method [16].

Results
The symptoms of DM are well known. The typical symptoms of DM include excessive thirst, blurred vision, bedwetting, frequent urination, lack of energy and fatigue, constant hunger and sudden weight loss [17]. However, it is important to be aware that symptoms of DM are not specific and may occur in other diseases as well [18-37]. Excessive thirst may occur in diabetes insipidus [18,19], hyponatremia [20], chronic hemodialysis [21], chronic heart failure [22] and schizophrenia [23]. Blurred vision symptom may occur in range of eye diseases [24]. Bedwetting may occur in range of urological diseases such as monosymptomatic nocturnal enuresis [25], pelvic floor disorders in women [26], urinary incontinence in men [27]. Lack of energy, fatigue may occur in some neurological disease [28], chronic liver disease [29], cancer [30] and as well as in depression [31]. Another symptom of DM such as constant hunger may occur in monogenic obesity and congenital generalized lipodystrophy [32], hyperthyroidism [33] or in anxiety [34]. Sudden weight loss also can happen after a stressful event, although it can be a sign of a serious illness such as hyperthyroidism [35], cancer [36] and depression [37].

Table 2 shows the frequency of glucose levels ≥ 200 mg/dL (≥ 11,1 mmol/mol) for NGM, PD and type 2 DM.

Table 2: The frequency of glucose levels ≥ 200 mg/dL (≥ 11,1 mmol/mol) for NGM, PD and DM type 2.

State of glucose metabolism	Total number of subjects	Subjects with glucose values ≥200 mg/dL	
		n	%
NGM	87	27	31.0
PD	41	30	73.2
DM	6	6	100

Those with DM had glucose level ≥ 200 mg/dl in 100% of cases. In PD glucose level 200 mg/dl and above had place in 73% of cases. In NGM 31% of subjects had discussable levels of plasma glucose. Hence, 57 subjects of total 128 investigated without DM (44.5%) had results ≥ 200 mg/dl (11,1 mmol/l).

Definition of specificity of given criteria [38] indicates that:

> **Specificity = true negative/ total number of well individual in population = 100 *60/87= 69.0%**

Table 3 shows the frequency of glucose levels ≥ 250 mg/dL (≥ 11,1 mmol/mol) for NGM, PD and DM type 2.

Table 3: The frequency of glucose levels ≥ 250 mg/dL (≥ 11,1 mmol/mol) for NGM, PD and DM type 2.

State of glucose metabolism	Total number of subjects	Subjects with glucose values ≥250 mg/dL	
		n	%
NGM	87	0	0
PD	41	0	0
DM	6	2	33.3

Those with DM had glucose level ≥ 250 mg/dl in 100% of cases. In cases with NGM and PD glucose values ≥250 mg/dL were absent.

Definition of specificity of given criteria [38] indicates that:

> **Specificity = 100*87/87= 100.0%.**

Diabetes classic symptoms analysis demonstrated their non specificity. Specificity of random plasma glucose ≥ 250 mg/dl was statistically highly significant ($p < 0.00001$) than random plasma glucose ≥ 200 mg/dl: 100% vs 69%.

Discussion

Establishing of DM diagnosis leads to serious psychological, social and economic consequences [5,7,13,17]. Our study showed that classic symptoms of DM may occur in range of other diseases and conditions. Perhaps, specificity of symptoms is not high. Maybe, specificity will increase with presence of symptoms combination, but it wasn't proved by any of current research. Moreover, indication for symptom combination variants is absent in all presence guidelines [5-11,14,15].

Necessity of strict approach to DM diagnostics is reflected in all existing DM recommendations. Three diagnostic tests for DM are currently recommended, including measurement of fasting plasma glucose, 2-hour (2-h) post-load plasma glucose after a 75 g oral glucose tolerance test (OGTT) and HbA1c [5]. DM diagnosis requires presence of [5-11,14,15]:

1. 2 criteria out of 3 (FG ≥ 126mg/dl; G2h ≥ 200 mg/dl; HbA1c ≥6.5%)
2. Two diabetic criteria out of three diagnostic values for anyone.

According to the results of our study, specificity of random glucose levels ≥ 200 mg/dl (11.1 mmol/l) was 69.0%. Considering non-specificity of classic symptoms of DM and taking into account that specificity of symptoms combination is unknown, it is crucial to use the maximal specific glucose parameter. Thus, demonstrated before, specificity of RPG ≥ 200 mg/dl cannot be sufficient. As limitation of our study, we could suggest the use of oral glucose tolerant test instead of glucose monitoring for 24 hours. However, in our opinion, glucose load tests similar to 75 gr glucose tolerant test continue to exist in real clinical setting. Due to the fact that, glucose level of 250 mg/dl didn't occur in subjects with NGM and PD in other words, had 100% specificity, we consider namely this level of glucose as appropriate diagnostic test. Glucose levels ≥ 250 mg/dl the same value that is associated with possibility of occurrence diabetic ketoacidosis [39]. Higher values are characterized with hyperosmolar state [40]. This level of glucose also is one of the fundamental values for assessment 24-hour glucose monitoring [41].

Therefore, in our opinion, diagnostic criteria for diabetes mellitus should be as follows:
1. FG ≥ 126 mg/dl
2. G2h ≥ 200 mg/dl
3. HbA1C ≥ 6.5%
4. In presence of classic symptoms of hyperglycemia RPG ≥ 250 mg/dl.

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