Identification of impaired fasting blood glucose and diabetes increases in healthy young adults after mentally demanding task

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Abstract: - The aim of the study was to investigate the influence of human functional state (in relative functional rest, after the night rest on fasting and during active mental activity) on the measurement of capillary blood glucose level in the diagnosis of carbohydrate metabolism disorders to avoid overdiagnosis (or even underdiagnosis) of "impaired fasting glucose" and "diabetes." The study was conducted with the participation of 27 males aged 20–29 years. The measurement was carried out using the glucose monitoring system “Rightest GM100” (Bionime, Switzerland) with an accuracy of up to 0.1 mmol/l. The first four measurements of blood glucose were conducted on the participants on fasting, approximately 10–16 hours after meal. On the first (initial) measurement of blood glucose, volunteers were in a state of functional rest (after the night rest). In the dynamics of mental work, fasting blood glucose measurements were conducted three times, after 2, 4, and 6 hours from the beginning of the study. After 30 minutes following the 4th measurement, glucose tolerance test was conducted. During glucose tolerance test, blood glucose was measured three times, precisely after 30, 60 and 120 minutes following oral intake of water (200 mL)–glucose solution (75 g) for each participant. The results showed that the number of identified "impaired fasting glucose" or even "diabetes" basically depends on the functional state of the participants. In the state of relative functional rest, "impaired fasting glucose" was detected in only one participant. In course of mental work, in 13 blood samples out of 80 samples taken (16.3 ± 4.2%; $p < 0.001$) glucose level exceeded the upper limit of normoglycemia and corresponded to the criterion of "impaired fasting glucose" (9 samples) or "diabetes" (4 samples) during mental work (37.0 ± 9.5%; $p < 0.001$). However, the glucose tolerance test did not reveal diabetes or impaired glucose tolerance. This indicates that when determining the fasting plasma glucose, it is important to standardize other conditions to avoid the influence of hyperglycemic effects, such as mental activity on fasting.

Key-Words: - Glucose, Glycemia, Fasting Blood Glucose, Diabetes, Functional State, Young Adults, Mental Task

1 Introduction

Disorders in carbohydrate metabolism have always posed a substantial level of problem to humans since antiquity. These disorders affect the biochemical processes responsible for the formation, breakdown and interconversion of carbohydrates in living organisms. Types of carbohydrate metabolic diseases include diabetes mellitus, lactose intolerance, fructose intolerance, galactosemia, glycogen storage disease, mucopolysaccharidoses. Some of the disorders are inborn errors of carbohydrate metabolism and are less common [1-3]. The most common types of carbohydrate metabolism disorders are acquired: diabetic ketoacidosis, hyperosmolar coma (hyperosmolar hyperglycemic state), and hypoglycemia. These three disorders could result from diabetes mellitus complication. Amongst the acquired carbohydrate metabolic disorders, diabetes mellitus as a type of carbohydrate metabolic disease to date is the most common metabolic disease that affects people worldwide [4-6]. Following its first most elaborate description in by the Greek physician, Aretaeus of Cappadocia during the 1st century AD [7,8] to the discovery by Frederick Banting, Charles Best, James Collip in the early 1920s of the first biochemical substance, known as at that time to be molecule, responsible for the disease development [9,10], numerous progress has been made in the identification of the causes and mechanisms of the disease. In spite of the huge progress made in the understanding of the ethio-pathogenesis and treatment of the disease, unfortunately, the number of people with the condition has continuously increased over the past decades. Recent reports indicate that the number of diabetic patients in the world increased from 150 million people in 2008 to 382 million in 2013 and it is projected to hit 592 million by 2035 [5,11]. In addition, prediabetic condition is projected to increase by 155 million reaching 471 million compared to the number of cases in 2013. The burden of diabetes is huge, causing about 5.1 million deaths and taking up some USD 548 billion dollars in health spending in 2013 alone. The sharp increase in the prevalence of diabetes, especially type 2, in all age groups, including children and adolescents [2, 7], was the basis for the review of the diagnostic criteria of the disease. The main diagnostic criterion of fasting blood glucose was reduced from 140 mg/dL (7.8 mmol/l) to 126 mg/dL (7.0 mmol/l) for blood plasma and to 110 mg/dl (6.1 mmol/l) for whole blood. A new predictor of "impaired fasting glucose" as a stage between normal glucose metabolism and diabetes was introduced [1, 2, 4, 5, 7]. Thus, current diagnostic criteria of normoglycemia on fasting for capillary whole blood

TABLE 1. Criteria for evaluation of concentration of glucose in plasma or whole blood by WHO (1999) [4, 5, 12, 13].

Study	Concentration of glucose, mg/dL (mmol/l):			
	Whole blood		Plasma	
	venous	**capillary**	venous	capillary
Diabetes mellitus				
Fasting	≥ 110 (≥ 6.1)	**≥ 110 (≥ 6.1)**	≥ 126 (≥ 7.0)	≥ 126 (≥ 7.0)
After 2 hours following glucose load (75 g)	≥ 180 (≥ 10.0)	**≥ 200 (≥ 11.1)**	≥ 200 (≥ 11.1)	≥ 220 (≥ 12.2)
Impaired tolerance to glucose				
Fasting	< 110 (< 6.1)	**< 110 (< 6.1)**	< 126 (< 7.0)	< 126 (< 7.0)
After 2 hours following glucose load (75 g)	≥ 120 (≥ 6.7) and < 180 (< 10.0)	**≥ 140 (≥ 7.8) and < 200 (< 11.1)**	≥ 140 (≥ 7.8) and < 200 (< 11.1)	≥ 160 (≥ 8.9) and < 220 (< 12.2)
Impaired fasting glycemia (hyperglycemia)				
Fasting	≥ 100 (≥ 5.6) and < 110 (< 6.1)	**≥ 100 (≥ 5.6) and < 110 (< 6.1)**	≥ 110 (≥ 6.1) and < 126 (< 7.0)	≥ 110 (≥ 6.1) and < 126 (< 7.0)
After 2 hours following glucose load (75 g)	< 120 (< 6.7)	**< 140 (< 7.8)**	< 140 (< 7,8)	< 160 (< 8.9)
Normal				
Fasting	< 100 (< 5.6)	**< 100 (< 5.6)**	< 110 (< 6.1)	< 110 (< 6.1)
After 2 hours following glucose load (75 g)	< 120 (< 6.7)	**< 140 (< 7.8)**	< 140 (< 7.8)	< 160 (< 8.9)

Note: Hours following the glucose load (75 g of glucose taken orally as an aqueous solution).

are less than 100 mg/dl (<5.6 mmol/l); impaired fasting glycemia (8 or more hours after meal) – 100-109 mg/dL; diabetes mellitus – 110 mg or more of glucose in 100 ml of blood (Table 1). In this case, the diagnosis of diabetes must be confirmed by re-measuring fasting blood glucose, as well as the results of glucose tolerance test (blood glucose levels after 2 hours following glucose load in an amount of 75 g).

However, problem of interpretation of the results of diagnostic tests in diabetes is reproducible glucose concentration due to the intra-individual variations of fasting plasma glucose at one and the same person [5] and the influence of factors that increase blood glucose and not related to the intake of carbohydrates [14-17]. Factors such as stress or mental activity through activation of the sympathetic division of the autonomic nervous system, stimulation of the secretion of counter-regulatory hormones and respectively the processes of gluconeogenesis and glycogenolysis can increase the level of fasting glucose [18, 19].

Inclusion of these factors in the diagnosis of disorders of carbohydrate metabolism is quite important due to the significant prevalence of operator (mental) forms of labor and the necessity of its execution at night (hence blood sampling, even in the morning hours may occur on the background of active functional state) [18-21]. The relevance of this approach is determined, in part, by the recommended reduction level of fasting glucose in whole blood to 110 mg/dL in the diagnosis of diabetes (Table 1). According to Zalutskaya and Mokhort (2001), of 35 patients with confirmed type 2 diabetes mellitus based on basal fasting glucose (twice), glucose tolerance test in 10 subjects did not confirm this diagnosis. The test result for these 10 people (28.6% of cases) was consistent with normoglycemia [22]. Based on these facts, we can reasonably assume that taking a blood sample for the determination of glucose in some patients, there is activation of glycolysis and / or gluconeogenesis. Likely, to exclude this phenomenon in more detail, it is necessary to standardize the conditions of blood collection, not only on an empty stomach (8 or more hours after a meal), but also to minimize the effect of physiological factors that increase blood glucose levels (in particular, during active mental activity).

The aim of this study was to investigate the need to consider human functional state when determining the level of glucose in capillary blood glucose (in relative functional rest/after the night rest on fasting and during active mental activity) in the diagnosis of disorders of carbohydrate metabolism to avoid overdiagnosis (or even underdiagnosis) states of "impaired fasting glucose" and "diabetes."

2 Methods

The Ethics and Research Committee of the Belarusian State Medical University, Minsk, Belarus approved the study protocol. The study was conducted with voluntary participation of 27 men aged 20–29 years, after the aims and objectives of the study had been explained. All participants were certified to be in good health condition. From the most recent medical history, participants had no prior history of diabetes or impaired glucose level or tolerance. Moreover, none of the participants drank alcohol for the past week. All participants gave written informed consent twice to participate in the study (1–2 weeks before the study and on the day of the study).

2.1 Inclusion criteria

1. Absence of any health problem based on recent medical examination.
2. Willingness to participate. Participants were told that they could withdraw at any phase of the experiment even if they started it.
3. No history of diabetes or glucose intolerance based on recent medical examination.
4. Alcohol abstinence of at least 1 week.
5. Participants were expected to have a good night sleep (for at least 10 hours) before the experiment.

2.2 Exclusion criteria

1. Presence of any health problem based on recent medical examination. On this basis, six participants were excluded.
2. Unwillingness to participate in the study.
3. A history of diabetes or glucose intolerance based on recent medical examination.
4. Recent consumption of alcoholic beverage of any kind during the past one week (based on Alcotest reading of 0.00 measured twice in each participant).
5. People using medications were also excluded.
6. Individuals who were drug users/abusers were excluded. Those who fail the drug abuse test or scored below 70% on the sincerity test, were excluded from the study.

The study began in $8^{00}/9^{00}$ and ended in $17^{00}/18^{00}$. In each study, 2 to 5 participants were involved. Determination of glucose in capillary blood from each participant was carried out 7 times. The first four measurements of blood glucose were performed on the participant on an empty stomach (10–16 hours after meal), when the main sources of glucose in the blood are gluconeogenesis and glycogenolysis in the liver. At the first (initial) measurement of glycemia, conducted at 8.00 am or 9.00 am, the volunteers were in a state of functional rest after the night rest. In the dynamics of mental work (fasting), blood glucose measurements were performed three times, namely, after 2 (2nd measurement), 4 (3rd measurement) and 6 (4th measurement) hours from the start of the study. After 30 minutes following the 4th glycemia measurement, glucose tolerance test was conducted. During blood glucose sampling, blood glucose level was measured three times, namely, 30 (5th measurement), 60 (6th measurement) and 120 (7th measurement) minutes after oral intake of water (200 mL water) glucose solution (in an amount of 75 g for each participant).

Measurement was carried out using a glucose monitoring system in the 1–3 ml of blood “Rightest GM100” (Bionime, Switzerland) with an accuracy of up to 0.1 mmol/l. The time spent on each subject in the study was 9 hours.

Mental load in all participants was completely identical and included two types of work – performance of standard tests to identify indicators of mental health and cognitive functions (memory, thinking and attention), as well as mental work to fill questionnaires and the analysis of educational texts. Tests for mental health and cognitive functions were carried out five times: immediately after each blood sampling and at baseline (1st test) and in the course of mental activities from 2 hours (2nd measurement), 4 hours (3rd measurement) and 6 hours (4th measurement). Questionnaires used in the study were: Well-being, Activity and Mood ("WAM" and "WAM-8" tests [23, 24]), State and Trait Anxiety Inventory [25, 26], “Neuro-psychological adaptation" test, "Sincerity" test, "Alcohol Use Disorders Identification Test", "Cut Down, Annoyed, Guilty and Eye Opener Test", "Michigan Alcohol Screening Test" and "Post-Alcohol Intoxication Syndrome" [27-29]. At the 2nd phase (also for 1 ½ h - 2 ½ to 4 h). Educational texts used were "Physiology and morphology of bone" and "Physiology of the autonomic nervous system". Detailed description of the tests and questionnaires is outlined in [29]. The average speed of information processing in the subjects was 2.65 symbols/second, which was 37.2% of the maximum average speed of viewing the symbols in the test "proof-correction probe" on attention (7.12 letters/second). The mental work was carried out immediately after every glucose measurement up to the first 4 glucose measurements. This study was not designed to determine the state of mental functioning; rather the mental work was intended to produce a different functional state for the participants that could provide a means for identifying pathological changes in blood glucose.

TABLE 2. Concentration of glucose in capillary whole blood glucose and its dynamics in conditions of prolonged mental work on fasting and after 2 h following 75 g glucose load and after rest

Average level of glucose in whole capillary blood (M±m), mg/dL					
Initial=27	After 2 h of mental work, n=27	After 4 h of mental work, n=27	After 6 h of mental work, n=26	After 2 h of glucose load, n=26
80.1±2.2	**87.3±1.8 ***	**86.2±2.2**	**81.7±3.8**	**93.2±2.0 ***
In relation to the initial	P<0.02; t=2.548;df=26	P>0.05; t=2.000;df=25	P>0.05; t=0.372;df=25	P<0.01; t=4.396;df=25

Statistical analysis of the results was carried out with the computer program “SPSS” (Statistical Package for the Social Science), version 16, using parametric and nonparametric Wilcoxon test and Student's t and Mann-Whitney test, Pearson and Spearman [30, 31].

3 Results

In a state of relative functional rest in 26 participants after fasting overnight, glucose in capillary blood ranged from 63 mg/dL (3.5 mmol/l) to 99 mg/dL (5.5 mmol/l), i.e. within normoglycemia (<100 mg/dL, Table 1). In one participant, blood glucose level exceeded the threshold of fasting normoglycemia and was 103 mg/dL (5.7 mmol/l), which corresponds to the criterion of "impaired fasting glucose" (Table 1).

Mental work of young people on an empty stomach, during the first 2 hours of activity in 89% of participants (24 people), was accompanied by increase in blood glucose and the average glucose level (Table 2). As a result, already in 4 participants, blood glucose levels exceeded the lower limit criterion of impaired fasting glucose by 1–8 mg. Thus, under conditions of 2-hour mental work on an empty stomach, identification of a positive criterion of "impaired fasting glucose" was not 3.7% of cases, but 14.8% ($t = 2.176$, $df = 27$, $p < 0.05$) of the entire group of 27 people.

At 4 and 6 hours of mental work, dynamics of blood glucose levels showed a significant reduction in 13 participants and a significant rise in the other group of 8 people. In 5 participants, dynamics of glycemia was less pronounced, and one man refused to continue the study and dropped out of the experiment, after the third blood sampling. In this regard, the average content of glucose in whole capillary blood for the entire group after 6 hours of mental work did not differ from the initial value (Table 2). However, immediately, in 6 (of 8) of the participants (23.1 ± 8.3% of cases, $t = 2.783$, $p < 0.01$ for 26 young people that continued the study) blood glucose level was 101–110 mg/dL, that exceeds the lower limit of the criterion of "impaired fasting glucose" at 1–10 mg. In 4 participants (15.4 ± 7.1% of cases, $t = 2.169$, $p < 0.05$) glucose was 110 mg/dl, which corresponds to capillary whole blood taken from a person on fasting, diabetes mellitus criterion (Table 1).

4 Discussion

The results of this study showed that the state of mental functioning is a determining factor for the identification of disorders in fasting blood glucose regulation or diabetes. Analysis of the results showed that the number of identified criteria of "impaired fasting glucose" or " diabetes mellitus" essentially depends on the functional state of the participant. In the state of relative functional rest, "impaired fasting glucose" was detected in 1 out of 27 of the participants (one of the 27 measurements of glucose or 3.7%). During mental work in 13 blood samples from 80 samples taken, glucose level exceeded the upper limit of normoglycemia and was consistent with the criterion of "impaired fasting glucose" (9 samples) or "diabetes mellitus" (4 samples). Thus already in 16.3 ± 4.2% ($t = 3.881$, $p < 0.001$) of the cases, diagnostically meaningful criteria were detected. During mental work on an empty stomach, these criteria were identified in 10 participants. Thus, 37.0 ± 9.5% ($t = 3.895$, $p < 0.001$) of the cases in patients may be related to detection of elevated blood glucose indicating hyperglycemia and the possible risk of diabetes. In 4 cases, hyperglycemia during mental work on an empty stomach reached the level of 110 mg/dL, which meets the criterion of "diabetes mellitus" on the WHO classification (Table 1). However, the glucose tolerance test after a glucose load of 75 g, after 2 hours, did not reveal high (greater than 200 mg/dL) or elevated (140–199 mg/dL) blood glucose levels, corresponding to the criteria "diabetes mellitus" or "increased glucose tolerance" (Table 1). The glucose content in the blood of participants at 2 hours after glucose load ranged from 74 to 115 mg/dL, an average of 93.2 mg/dL (Table 2). Thus, the conducted test excluded in all participants, not only diabetes, but also impaired glucose tolerance. At the same time, 71.4% of cases are confirmed in older people (35–84 years) with verified criterion for diabetes in terms of fasting glucose tolerance test [22]. In 28.6% of cases in older adults, results of glucose tolerance test do not confirm the diagnosis of diabetes in patients with confirmed diagnosis of type 2 diabetes, according to the fasting glucose [22].

Numerous reports have indicated that recommended tests for glucose such as glycated hemoglobin concentration (HbA1c) test miss a substantial number of potential candidates with diabetes [32]. The relatively insensitive of fasting plasma glucose in the detection of diabetes has been reported in other studies [33, 34]. Although the simultaneous measurement of fasting plasma glucose and HbA1c had been reported to be a more sensitive and specific screening tool for identifying high-risk individuals with diabetes and “impaired glucose tolerance” at an early stage, a report by [33, 35] has shown that oral glucose tolerance test is more accurate.

Based on results of fasting plasma glucose and HbA1c, 33% of diabetic subjects and 75% of those with impaired glucose tolerance that were misclassified as euglycemic had diabetes and impaired fasting glucose respectively according to oral glucose tolerance test [33]. More recently, María José Picón et al. (2012) showed that the HbA1c test criterion alone or in combination with fasting glucose test criterion does not provide a sensitive and specific diagnosis of abnormal carbohydrate metabolism (compared with oral glucose tolerance test) [36]. Although prediction model has been developed, in addition to using fasting and 2-hour plasma glucose levels, several indices including medical history, body mass index, blood pressure, fasting serum total, low-density lipoprotein, and high-density lipoprotein cholesterol and triglyceride levels are analyzed, thereby leading to slight improvement and hence, greater cost and inconvenience [37]. There is possibility that, apart from clinical indices outlined, other influences on fasting blood glucose could result in misdiagnosis of diabetes mellitus or impaired fasting blood glucose. This indicates that when determining the fasting glucose, it is important to standardize other conditions to avoid the influence of such factors as mental activity (fasting) on glycemia.

The obtained evidence in our study suggests the need to consider human functional state when assessing glucose content of whole capillary blood. This is especially true in connection with the prevalence of operator work (which is also carried out at night). It may be necessary to consider better standardization during blood glucose sampling (not only on an empty stomach, but also in terms of mental and emotional rest) or on lifting the upper limit of normal glucose in capillary whole blood glucose.

Limitations of this study: The study was conducted on participants of the same sex; the data need to be confirmed by representatives of the female sex.

The study is of great practical importance in the daily monitoring of blood glucose, including the study of the dynamics of glucose in a fasting working person and during rest. The establishment of duration of hyperglycemia after mental activity is required.

5 Conclusion

Signs of increased glucose level in capillary whole blood can be detected in a healthy person with a frequency of 3.7% (in state of relative functional rest) to 37.0% (during mental activity on fasting) following 10–16 hours after meal). This fact must be taken into account to avoid overdiagnosis of "increased fasting glucose" or "diabetes mellitus", which can be achieved by a better standardization during blood sampling.

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