



Application of a New Method of Noninvasive Assessment of Carbohydrate Metabolism Disorders in the Population Screening

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Abstract. Method for conducting a non-invasive screening of the population for carbohydrate metabolism disorders (CMD) has been developed and described. The novelty of the method is that there are no medical standards in the field of endocrinology for the non-invasive type of screening, so the method was based on the results of a clinical study of electrocardiographic abnormalities in patients with CMD, where the method of non-invasive determination of CMD by first-lead ECG was used. During the development of the method, an additional analysis of the ECG sample obtained during the study was performed. As a result of the analysis, it was concluded that the effectiveness of the method (sensitivity and specificity) vary slightly depending on the time of taking an ECG during the day. This means that the patient can come to the screening using the new method of non-invasive detection of CMD not only in the morning and not necessarily on an empty stomach, in contrast to the invasive methods (fasting plasma glucose test and oral glucose tolerance test). To make a decision «there is a suspicion of CMD /there is no suspicion of CMD», the patient only needs to take up to 2 ECGs.

Keywords: first-lead ECG; type 2 diabetes (T2DM); carbohydrate metabolism disorders (CMD)

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Применение метода неинвазивного оценивания нарушений углеводного обмена при скрининге населения

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Аннотация. Разработана и описана методика проведения неинвазивного скрининга населения на нарушение углеводного обмена (НУО). Новизна методики заключается в том, что по неинвазивному типу скрининга еще не существует медицинских стандартов в области эндокринологии, поэтому методика составлялась на основе результатов клинического исследования по изучению электрокардиографических отклонений у больных с НУО, где использовался метод неинвазивного определения НУО по ЭКГ первого отведения. Во время разработки методики был проведен дополнительный анализ выборки ЭКГ, полученной в ходе исследования. В результате анализа сделаны выводы, что показатели эффективности метода (чувствительность и специфичность) слабо изменяются в зависимости от времени съема ЭКГ в течение суток. Это означает, что пациент может явиться на скрининг по методике неинвазивного определения НУО не только утром и не обязательно натощак, в отличие от инвазивных методик (тест глюкозы плазмы натощак и пероральный тест толерантности к глюкозе). Для принятия решения «есть подозрение на НУО»/«нет подозрения на НУО» пациенту достаточно снять до 2 ЭКГ.

Ключевые слова: ЭКГ первого отведения; сахарный диабет 2 типа

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1. Introduction

Diabetes mellitus (DM) is a disease that is constantly spreading throughout Russia and the whole world [3,4]. According to the 2016 NATION study [5]: «Approximately one in five adult Russians had pre-diabetes, 5.4% had T2DM and about half of the diabetic subjects were previously undiagnosed». Type 2 diabetes mellitus (T2DM) is the main disease associated with disordered carbohydrate metabolism (CMD).

The process of developing T2DM is quite long and unnoticeable for the patient. The early stage of carbohydrate metabolism disorders on the average lasts from 5 to 10 years [6]. As a rule, the patient evaluates his condition for the presence of CMD too late, for example, when he has been suffering from T2DM for a long time. For an early detection of CMD, a periodic screening of the population at risk is carried out. Methods that can be used for screening should include those that meet the following requirements:

- easy to perform;
- security;
- standardization;
- low cost;
- reliability

The medical recommendations [2, 7] indicate that an oral glucose tolerance test (OGTT) with 75 g of glucose, a fasting plasma glucose (FPG) test, or a blood test for glycated hemoglobin should be used as a screening test. The disadvantages of these tests include the following:

- invasiveness – in order to obtain blood that measures the level of glucose or glycated hemoglobin, the patient needs to have his skin pierced;
- high cost-these tests require consumables materials (disposable needles, for OGTT - containers with 75 g of glucose, etc.), and it is also necessary to pay for the work of laboratories to analyze the collected blood samples;
- complexity of implementation – the test requires qualified medical personnel and specialized equipment. This means that in practice, these tests can only be taken in city clinics, hospitals and medical laboratories, since there are usually no properly qualified personnel and/or the necessary reagents and equipment for blood analysis in paramedic-midwifery centers (PMC). Therefore, the rural population will have to go to the nearest city medical facility to undergo a full-fledged CMD screening. In addition, to obtain reliable results of OGTT with 75 g of glucose and the FPG test, the patient must come to the screening in the morning and on an empty stomach.

Now, Russia does not yet have medical standards and recommendations for a non-invasive CMD screening, which could compensate for the shortcomings described above.

The paper [1] describes a research devoted to the study of electrocardiographic abnormalities in patients with CMD, conducted under the supervision of A.M. Mkrtumyan, MD.

The study obtained and analyzed a sample consisting of:

- 1997 first-lead ECGs taken from 127 patients with T2DM;
- 741 first-lead ECGs taken from 59 patients without T2DM.

All ECGs were taken in hospitals setting in two medical institutions: Moscow City Clinical Hospital 52 and The Loginov Moscow Clinical Scientific Center.

ECGs were taken using a portable CardioQVARK electrocardiograph [8] (registration certificate no. 2019/8124 dated February 15, 2019), then analyzed for the presence of a cardio sign of CMD with the help of an expert decision support system for taking decision by an endocrinologist developed by the company «EC-leasing» (ES DM), using the method of determining CMD described in the patent [9,10]. According to the results of the study, the sensitivity of the method for one ECG was 70%, and the specificity was 86%.

2. Setting up the problem

The aim of this research work was to develop a method for conducting a non-invasive screening of the population for the CMD based on data and results obtained in the course of a clinical study [1].

To achieve this goal, one must complete the following tasks:

- analyze the data to determine what time of the day the patient should be screened using a non-invasive method, and whether it should be performed on an empty stomach;
- develop a process for conducting a non-invasive CMD screening;
- compare the method of non-invasive detecting of CMD by OGTT with 75 g of glucose, a FPG test and a blood test for glycated hemoglobin according to the criteria for meeting the screening requirements.

3. Preliminary analysis of the sample

Before developing a screening method, it was necessary to determine at what time of the day the patient should take an ECG, and whether it should be done on an empty stomach, so that the

reliability of the method of non-invasive determination of the CMD does not suffer. To do this, we will perform an additional statistical analysis on the ECG sample obtained during the study [1].

Let us clarify the requirements for the time of screening. For that purpose, we will calculate the sensitivity and specificity of the method of non-invasive determination of the CMD for different times of taking the ECG during a day. In accordance with the study protocol [1], the patients with CMD had an ECG taken:

- before breakfast on an empty stomach;
- 2 hours after breakfast;
- before dinner;
- 2 hours after lunch;
- before dinner;
- 2 hours after dinner.

Table 1. Comparison of sensitivity and specificity of the method of noninvasive assessment of the cmd depending on the time of taking the ECG

Time of ECG taking relative to food intake	Sensitivity (1 ECG each)	Specificity (1 ECG each)
Before breakfast on an empty stomach	70% (246 out of 353 ECGs taken by patients with T2DM had a cardiosign of CMD)	88% (190 out of 216 ECGs taken by patients without T2DM did not show a cardiosign of CMD)
2 hours after breakfast	73% (248 out of 341 ECGs taken by patients with T2DM had a cardiosign of CMD)	91% (189 out of 207 ECGs taken by patients without T2DM did not show a cardiosign of CMD)
Before lunch	74% (253 out of 340 ECGs taken by patients with T2DM had a cardiosign of CMD)	89% (159 of 178 ECGs taken by patients without T2DM did not show a cardiosign of CMD)
2 hours after lunch	75% (155 out of 206 ECGs taken by patients with T2DM had a cardiosign of CMD)	83% (64 out of 77 ECG taken by patients without T2DM, did not show a cardiosign of CMD)
Before dinner	80% (336 out of 421 ECGs taken by patients with T2DM had a cardiosign of CMD)	84% (21 out of 25 ECGs taken by patients without T2DM did not show a cardiosign of CMD)
2 hours after dinner	83% (280 of 336 of the ECG taken by the patients with DM2, had a cardiosign of CMD)	87% (33 out of 38 ECGs taken by patients without DM2 did not show a cardiosign of CMD)

Table 1 shows the results of calculations of the sensitivity and specificity of the method of noninvasive determination of CMD by ECG taken at different times of the day. One can see that the sensitivity for different times of taking the ECG per day varied the sensitivity in the range of 76±6%, and the specificity – in the range of 87±4%. This in turn means the following:

- for the patient, it does not matter what time to come for a non-invasive screening. He can appear in the morning or in the afternoon;
- the patient does not have to come for a non-invasive screening on an empty stomach.

Next, we will calculate the maximum number of required repeated ECG readings per patient, so that each subsequent measurement can improve the accuracy of the screening result («the patient has a suspicion of CMD»/ «No suspicion of CMD»).

To do this, the first 3 ECGs taken by each patient with and without T2DM were taken from the sample (a total of 558 ECGs), then a decision tree was compiled using IBM SPSS Statistics software. The dependent variable of the tree is the sign «there is a suspicion of CMD in the patient» / «there is no suspicion of CMD», independent:

- a manifestation of a cardiosign of CMD on the first ECG of the patient («Yes/no»);
- a manifestation of a cardiosign of CMD on the second ECG of the patient («Yes/no»);
- a manifestation of a cardiosign of CMD on the third ECG of the patient («Yes/no»).

The result of building the tree is shown in fig. 1.

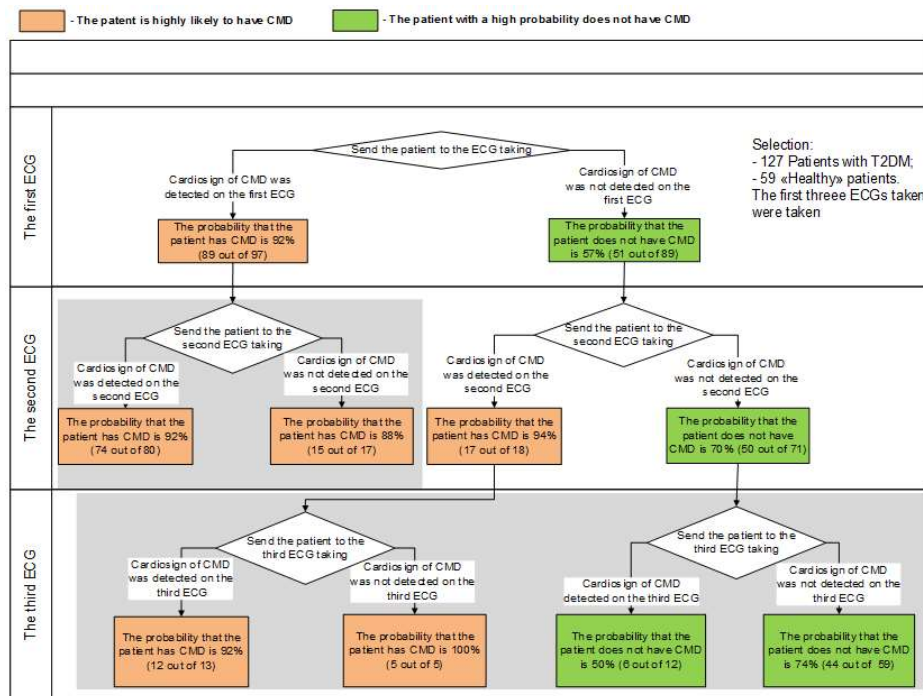


Fig. 1. The tree of taking decision whether the patient has CMD

The decision on the presence or absence of a CMD at each stage was made based on the probability of which option is higher. If at the next stage, the decision was made regardless of whether the cardiosign of the CMD is shown on the ECG or not, the stage was considered meaningless (in Figure 1, highlighted in gray). In total, to achieve maximum accuracy of the screening result, it is sufficient to take no more than 2 ECGs.

4. Description of the screening process

According to the method of non-invasive determination of CMD, screening is divided into 3 stages: ECG taking, ECG processing, and decision-making on the patient.

The ECG is taken where the patient is located. This means that the patient can be screened both in city clinics, in the PMC, or even at home. The main thing is that there should be a portable electrocardiograph on the spot that can transmit the taken ECG over the Internet for further processing.

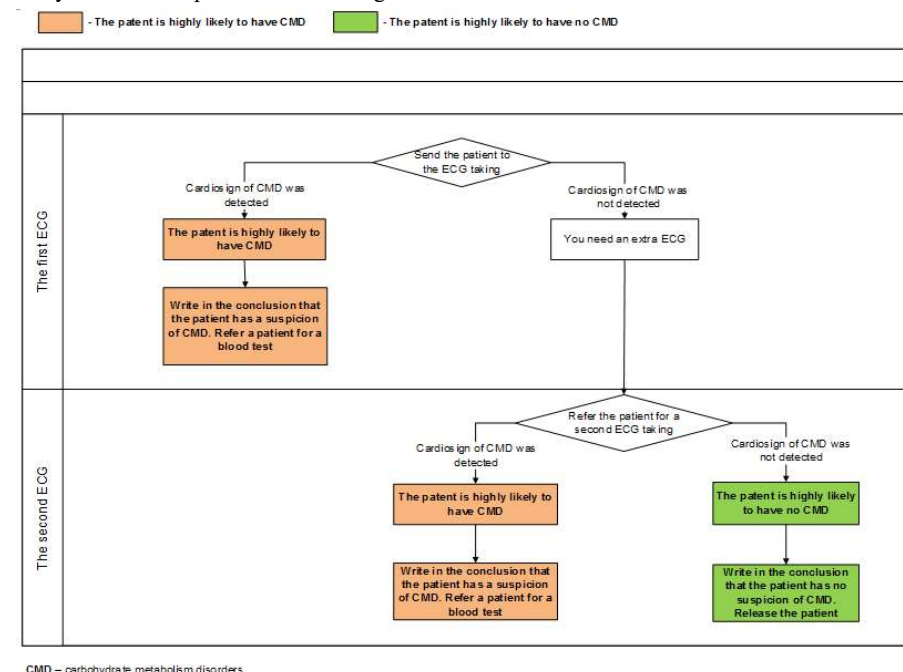
The ECG processing was performed automatically in a separate computer center using the method of non-invasive detection of CMD. The results of processing the ECG and the value of cardio sign CMD are sent to the endocrinologist.

The decision on the patient «there is a suspicion of CMD/There is no suspicion of CMD» is made by an endocrinologist based on the results of ECG processing using a computer.

There are no requirements for the availability of medical laboratories at any stage of screening using this method, in contrast to invasive methods, where specialized equipment and laboratory conditions are required for the analysis of collected blood samples. The requirements for the number of qualified medical personnel involved have also been reduced:

- at the stage of taking the ECG, the presence of a medical professional is optional;
- it is only necessary to explain to the patient how to use a portable electrocardiograph, and track the correctness of the ECG taking process. If the patient has such an electrocardiograph with him, and he knows how to use it, then a medical personal is not required at the stage of taking the ECG;
- during the processing phase of the ECG no medical personal or laboratory is required;
- a qualified doctor is only needed at the stage of taking a decision on the patient. Moreover, thanks to the automated receipt of the patient's data and the ECG processing results, it is possible to serve the number of patients by an order more than it could be served during the screening process using the invasive methods.

The process of screening based on the method of assessing the CMD [1] and the results of statistical analysis of the sample are shown in Fig. 2.



CMD – carbohydrate metabolism disorders

Fig. 2. The algorithm for screening process using a non-invasive method of evaluating the CMD

4.1 First take of the first lead ECG

The first-lead ECG is taken using a portable electrocardiograph. After taking the ECG is sent for processing to the computing center, where a response is received in the form of SMS to the phone of the patient and messages are sent to the endocrinologist about the detected/undetected cardiosign of the CMD. If a cardiosign is detected, the endocrinologist concludes that the patient has a suspicion

of CMD, and gives him recommendations for the diagnosis of T2DM in combination with current medical standards [2] and referral to a blood test (OGTT with 75 g of glucose, analysis for glycated hemoglobin and/or fasting plasma glucose test of the doctor's choice). In case of non-detection of a cardiosign of the CMD, the doctor will direct the patient to re-take the ECG.

4.2 Second take of the first lead ECG

The ECG is also taken using a portable electrocardiograph. After reading, the obtained ECG is sent for processing to the computer center, where it receives a response in the form of an SMS to the patient's phone number and in the form of an appeal to the endocrinologist about the detection/non-detection of a cardiosign of CMD in patient's ECG. If the cardiosign is detected, the endocrinologist concludes that the patient has a suspicion of CMD, and gives him recommendations for the diagnosis of T2DM in combination with current medical standards [2] and referral to a blood test (OGTT with 75 g of glucose, analysis for glycated hemoglobin and/or fasting plasma glucose analysis at the doctor's choice). In case of non-detection of cardio sign of CMD, the endocrinologist writes in the conclusion that the patient has no suspicion of CMD, and gives him a recommendation to undergo screening again in a year.

The results of a comparison of the use of invasive methods and the method of non-invasive screening for CMD presented in this paper are presented in Table 2.

Table 2. Comparison of sensitivity and specificity of the method of noninvasive assessment of the CMD depending on the time of taking the ECG

Comparison criteria	OGTT with 75 g of glucose	FPG test	Blood test for glycated hemoglobin	Method of noninvasive assessment of the CMD
Ease of execution	Qualified personnel and laboratories are required at the stage of analysis of collected blood. The patient should come to the screening in the morning on an empty stomach	Qualified personnel and laboratories are required at the stage of analysis of collected blood. The patient should come to the screening in the morning on an empty stomach	Qualified personnel and laboratories are required at the stage of analysis of collected blood	At the stage of ECG processing, medical staff and laboratories are not required. The patient does not have to come to the screening in the morning on an empty stomach
Safety	Risk of complications due to invasiveness	Risk of complications due to invasiveness	Risk of complications due to invasiveness	Risks of complications associated with invasiveness are excluded
Standardization	Standardized [2]	Standardized [2]	Standardized [7]	Not yet standardized
Cost	High (expenses for medical laboratories, disposable blood collection materials)	High (expenses for medical, laboratories, disposable blood collection materials)	High (expenses for medical laboratories, disposable blood collection materials)	Low (one only need to buy sets of portable electrocardiographs, consumables)
Reliability	High	High	High	Testing is required

The results of the comparison show that the method of non-invasive assessment of the CMD is not yet prescribed in medical recommendations and standards. Since the study [1] was conducted in a

hospital setting on a fairly small sample of patients (less than 3000), it is necessary to conduct a separate clinical trial of the method for a more accurate assessment of its reliability in real screening. Due to its ease of implementation, low cost of the test, and noninvasiveness, this technique can be used as an adjunct to the recommended screening tests [2, 7]: OGTT with 75 g of glucose, FPG test, and blood analysis for glycated hemoglobin. Screening using a non-invasive method will allow both to reach a larger number of the covered population at the same time, and to specify which part of the population should undergo a regular invasive screening test.

5. Conclusion

The subject of research in this paper is a non-invasive screening of the population for type 2 diabetes. There are no medical standards in the field of endocrinology for the non-invasive type of screening, so the method is based on the results of a clinical study of electrocardiographic abnormalities in patients with disordered carbohydrate metabolism, where the method of non-invasive determination of CMD by the first-lead ECG was used [1]. The performance indicators of the method of noninvasive determination of CMD for one ECG differ depending on the time of taking the ECG as follows:

- the sensitivity[11] of the method is 70-83% (with the specified sensitivity, regardless of the ECG time taking is 70% [1]);
- the specificity[11] of the method is 83-91% (with the specified sensitivity, regardless of the ECG time taking is 86% [1]);

This means that the requirements for the patient to participate in a non-invasive screening have been reduced – the patient can attend the screening not only in the morning and not necessarily on an empty stomach. In addition, to make a decision by an endocrinologist about the presence/absence of suspicions of CMD, it is enough for the patient to take up to 2 of ECGs.

Based on the data from the study [1] and the results of additional analysis of a sample from the same study, a method for conducting a non-invasive screening of CMD was developed and described. It can become the basis for the development of a new standard for conducting CMD screening. Further testing of this technique is planned.

In the future, the use of non-invasive detection of CMD will significantly reduce the cost of the screening process and make it safer and easier to perform for patients in both urban and rural areas, reduce the requirements for the involvement, safety and qualification of medical personnel who conduct screening and process its results.

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