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Research Article

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Diagnosis of Diabetes Mellitus and Its Metabolic Variants in An Intravenous Glucose Tolerance Test

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Abstract

Using the developed mathematical model of glucose kinetics, the data of the intravenous glucose tolerance test (VTTG) obtained from 67 non-diabetic individuals, 27 patients with DM2 and 13 patients with DM1 were processed. The developed method of processing intravenous GGT data allows not only to unambiguously separate patients with DM and those without DM, but also to assess the severity of carbohydrate metabolism disorders and, as well as to identify DM only at the stage of glucose kinetics disorder, that is, before glucose kinetics disorders lead to the development of hyperglycemia. The intravenous GGT data analysis method allows for separate monitoring of glucose production by the liver and its elimination from the blood of the subject, which opens up new opportunities in the selection of hypoglycemic drugs and evaluation of their efficacy. In particular, regimens for prescribing hypoglycemic therapy in DM have been proposed, depending on the four glucose kinetics variants diagnosed in intravenous GGT. Two case studies show how prescribed hypoglycemic drugs affect the rate of glucose excretion from the blood in intravenous GGT (case study 1), as well as how a disorder of glucose kinetics parameters manifests itself before the development of hyperglycemia (case study 2).

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Introduction

When the initial clinical manifestations of diabetes mellitus (DM) and blood glucose levels do not clearly indicate the presence of DM, an oral glucose tolerance test (OGTT) is performed to clarify the diagnosis [1]. However, a significant limitation of diagnosing DM using OGTT is that blood glucose levels are substantially influenced by the process of glucose absorption in the gastrointestinal tract, which is unrelated to insulin action. Meanwhile, the essence of DM diagnosis lies in detecting insulin deficiency, not impaired glucose absorption. This limitation is overcome by the intravenous glucose tolerance test (IVGTT), in which glucose is administered intravenously, allowing the assessment of carbohydrate metabolism disturbances based on glucose kinetics parameters.

Despite this, IVGTT is not currently used for DM diagnosis because previously proposed methods for processing IVGTT results failed to distinguish between individuals with diabetes and healthy individuals [2]. In response, complex glucose kinetics models incorporating insulin concentration behavior during the test were proposed for DM2 diagnosis [3]. However, these models did not find clinical application due to the complexity of data collection and the lack of clear advantages over OGTT.

Given these considerations, a new method for analyzing glucose kinetics in IVGTT has been proposed. This method not only allows for the clear identification of individuals with DM but also simultaneously evaluates the rate of glucose elimination from the blood and glucose production by the liver during the test [4–9].

This study presents the results of applying the new method to IVGTT data obtained from healthy individuals and patients with DM. A computer program was developed for calculating glucose kinetics parameters in IVGTT. The program automatically determines the rate of glucose elimination from the blood and glucose production by the liver based on IVGTT data. It is available at www.diabet.ru.

Methods

Using the developed mathematical model of glucose kinetics, IVGTT data were processed from 67 individuals without DM, 27 patients with DM2, and 13 patients with DM1 (all participants provided informed consent to participate in the study). The IVGTT was performed using 25 g of glucose solution in saline, administered intravenously over 4 minutes.

Blood samples for glucose measurement were collected from a vein after an overnight fast and then every 8 minutes from the start of glucose administration: at 8, 16, 24, 32, 40, 48, and 56 minutes for individuals without DM and at 8, 16, 24, 32, 40, 48, 56, 64, and 72 minutes for individuals with DM [10]. The glucose kinetics parameters were calculated separately for each IVGTT.

The method for the mathematical calculation of glucose kinetics parameters in IVGTT was described in detail earlier [9]. The following glucose kinetics parameters in IVGTT were determined:

- **K-index** (% mmol/L/min): the rate of glucose elimination from the blood;
- **H-index** (mmol/L): the blood glucose concentration in IVGTT maintained by glucose production in the liver;
- **D1-index** ("diabetic index," arbitrary units): an indicator of the presence of DM and the degree of carbohydrate

metabolism impairment. A negative or zero value indicates no DM, whereas a positive value indicates DM. The higher the value, the greater the carbohydrate metabolism impairment

- **D2-index** (an index distinguishing between patients with moderate and severe hyperglycemia): a negative value indicates moderate hyperglycemia, while a positive value indicates severe hyperglycemia.

Results

The mean values of the H- and K-indices calculated from IVGTT data are presented in the table. The average rate of glucose elimination in the test (K-index) was lower with higher mean fasting glucose levels or higher values of the D1-index, which reflects the degree of carbohydrate metabolism impairment (see Table).

Table: Parameters of glucose kinetics in intravenous GTT in patients without DM, as well as in DM1 and DM2.

Parameters		Individuals without DM	Patients with DM2	Patients with DM1
		n=67	*n=27*	*n=13*
Fasting glycemia, mmol/L	M±m	5,2± 0,6	6,4±1,3	11,1±2,8
	Min-max	4,2–7,0	4,4–8,9	7,5–17,9
	Range: 5–95 percentile	4,3–6,6	5,0–8,6	8,2–15,9
K-index, 100*mmol/L/min	M±m	2,5±0,6	1,3±0,6	1,0±0,6
	Min-max	1,2–4,2	0,5–2,7	0,1–1,9
	Range: 5–95 percentile	1,7–3,8	0,8–2,4	0,1–1,8
H-index, mmol/L	M±m	3,1±1,7	3,9±3,2	10,1±4,1
	Min-max	0,0–6,8	0,0–8,9	0,0–17,9
	Range: 5–95 percentile	0,0–5,4	0,0–8,6	3,9–14,8
D_1-index (distance P(K,D) to the curve H_1 (K)), conventional units	M±m	-0,77±0,45	0,79±0,62	3,89±2,17
	Min-max	-0,02 to -2,07	0,00–2,16	0,96–9,47
	Range: 5–95 percentile	-0,09 to -1,8	0,13–1,97	1,48–6,93
D_2-index (distance P(K,D) to the curve H_2 (K)), conventional units	M±m	нет	-0,8±0,44	1,43±1,81
	Min-max		от -0,04 до -1,62	0,05 — 6,81
	Range: 5–95 percentile		от -0,17 до -1,48	0,06 — 4,11

This outcome is expected because fasting blood glucose levels reflect the severity of insulin deficiency. With significant insulin deficiency, glucose utilization by insulin-dependent tissues decreases, leading to a proportional reduction in the glucose elimination coefficient (K-index) as fasting glucose levels increase.

As shown in the table, the glucose production indicator in the test (H-index) increases with higher fasting glucose levels. This phenomenon aligns with the understanding of the liver's role in glycemic regulation. Fasting blood glucose levels are maintained exclusively by hepatic glucose production, which depends on insulin deficiency—the greater the deficiency, the higher the glucose production by the liver, as insulin suppresses hepatic glucose production.

Thus, the obtained IVGTT glucose kinetics data reflect current concepts of glycemic regulation in normal conditions and in diabetes mellitus (DM). However, the K-index alone does not allow for a definitive distinction between individuals with and without DM, as its values can overlap in both groups (see Fig. 1). For instance, a K-index value of 1.5 may be observed in both non-diabetic individuals and those with DM. This issue was encountered by diabetologists attempting to implement IVGTT in clinical practice (Ikkos). They hypothesized that the K-index could not be accurately calculated without considering hepatic glucose production, but they were unable to develop a method for assessing hepatic glucose production in IVGTT.

In contrast, our approach successfully evaluates hepatic glucose production (H-index); however, even these values alone do not provide a clear distinction between diabetic and non-diabetic individuals. Therefore, it was suggested that only the simultaneous consideration of K- and D-index values could reliably differentiate these groups. For this purpose, a two-dimensional glucose kinetics parameter was introduced, incorporating both the K-index and D-index values for each subject. This parameter can be represented as a point P(K,D) on a two-dimensional graph, where K-index values are plotted on the x-axis and D-index values on the y-axis (see Fig. 1).

As shown in Fig. 1, representing IVGTT glucose kinetics data as the two-dimensional parameter P(K,D) allows for highly reliable differentiation not only between individuals with and without DM but also between those with DM1 and DM2.

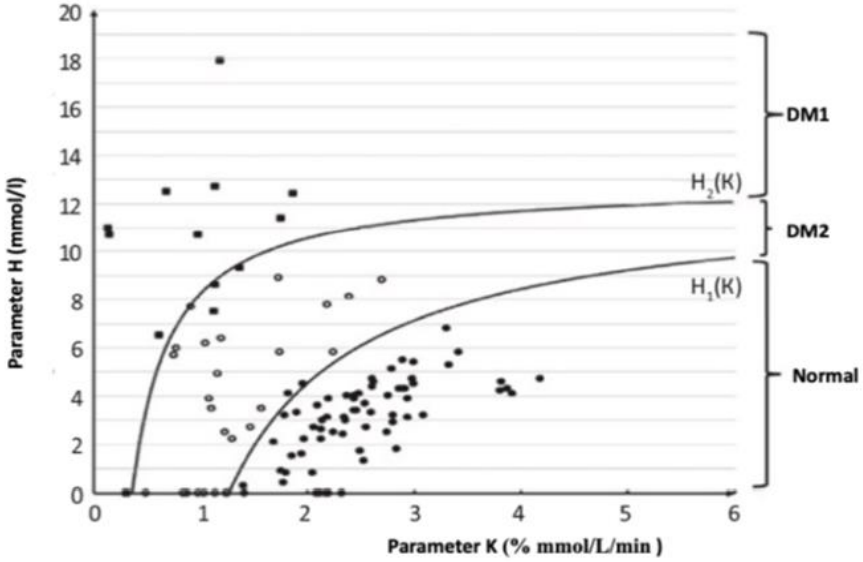

Figure 1: The graph shows the points P(K,D), which represent a two-dimensional parameter of glucose kinetics. The curve H (K) separates the points P(K,D) for patients without DM (black circles under the curve) from the other points for patients without DM (other points). The curve H (K) separates the two-dimensional parameters of glucose kinetics P(K,D) of patients with DM2 from the parameters of patients with DM1.

Based on the above, the proposed method enables an easy diagnosis of DM using IVGTT data: if the P(K,D) point of an individual lies below the H1(K) curve, the individual does not have DM; if it lies above the curve, DM is present. This can also be determined using the D1-index (which reflects the distance of the P(K,D) point from the H1(K) curve): a negative value (point below the H1(K) curve) indicates the absence of DM, while a positive value (point above the curve) indicates the presence of DM.

Moreover, IVGTT data can be used to determine the degree of glycemic regulation impairment: the higher the D1-index value, the more severely carbohydrate metabolism is disrupted.

The H2(K) curve can also be used to assess the severity of carbohydrate metabolism impairment in DM. If the P(K,D) point lies above this curve, the patient with DM is likely experiencing absolute insulin deficiency that is uncompensated by insulin. If the point lies below the curve, the deficiency is either relative or compensated absolute insulin deficiency. The numerical parameter representing insulin deficiency is the D2-index: a positive value indicates absolute insulin deficiency, while a negative value indicates relative insulin deficiency. The greater the positive value of the D2-index, the more severe the insulin deficiency.

As shown in Figure 1, the P(K,H) point falls into the DM zone (above the discriminant H1(K) curve) not only when both glucose kinetics parameters, K- and H-indices, deviate from the norm but also when at least one of these indices is outside the normal range. Based on this, the following classification of glucose kinetics impairment in IVGTT can be proposed:

- **Variant I (Isolated reduction in glucose elimination):** Only the rate of glucose elimination (K-index) is reduced. This was observed in 3 (23%) out of 13 patients with DM1 and in 17 (63%) out of 27 patients with DM2.
- **Variant II (Isolated increase in hepatic glucose production):** Only hepatic glucose production (H-index) is elevated. This was observed in 8 (62%) out of 13 patients with DM1 and in 8 (30%) out of 27 patients with DM2.
- **Variant III (Combined impairment of glucose kinetics in IVGTT):** Both hepatic glucose production (H-index) is elevated, and glucose elimination rate (K-index) is reduced. This was observed in 2 (15%) out of 13 patients with DM1 and in 8 (7%) out of 27 patients with DM2.
- **Variant IV (Borderline impairment of glucose kinetics in IVGTT):** Hepatic glucose production and glucose elimination rate are within the normal range, but their combination places the patient in the DM zone (above the discriminant H1(K) curve). This was observed only in DM2 in 2 (7%) out of 27 cases.

Given the wide range of mechanisms of action of modern antidiabetic drugs, the identified variants of glucose kinetics in IVGTT can improve the selection of appropriate treatment for diabetic patients and help assess the specific effects of the prescribed drugs. For example:

- **Variant I:** When glucose elimination (K-index) is reduced in DM2, treatment can begin with SGLT2 inhibitors (gliflozins), which increase glucose excretion by stimulating glucosuria (see clinical example below), or with metformin, which reduces insulin resistance.
- **Variant II:** When hepatic glucose production (H-index) is elevated in DM2, drugs that suppress it should be prescribed. These include GLP-1 receptor agonists (GLP-1 RAs) or DPP-4 inhibitors. In DM1, hyperglucagonemia contributes to increased hepatic glucose production. If a patient with DM1 has an elevated H-index despite insulin therapy, adding a GLP-1 RA to the regimen may be beneficial.
- **Variant III:** When both hepatic glucose production is elevated and glucose elimination is reduced (H-index and K-index) in DM2, a combination of drugs should be used: one that increases glucose excretion (SGLT2 inhibitors) and another that reduces hepatic glucose production (GLP-1 RAs). Insulin has a dual action—it simultaneously increases glucose utilization by peripheral insulin-

dependent tissues and decreases hepatic glucose production. Therefore, if insulin therapy is indicated for a patient with DM (positive D2-index), the prescribed insulin therapy will simultaneously reduce hepatic glucose overproduction and accelerate glucose elimination from the blood. For patients with DM2 who do not require insulin therapy (negative D2-index), sulfonylureas that stimulate insulin secretion may be prescribed.

- **Variant IV:** When glucose kinetics impairments are present but not detected by OGTT (DM2 at the stage of glucose kinetics disturbance without hyperglycemia yet, see Clinical Observation 2), preventive measures to delay the onset of overt DM are recommended. These include adopting a healthy lifestyle, such as a diabetic diet that restricts refined carbohydrate intake (e.g., sugar). Alternatively, it may be worth prescribing one of the new antidiabetic drugs (GLP-1 RAs, DPP-4 inhibitors, or SGLT2 inhibitors), which may suffice to normalize glucose kinetics parameters in IVGTT.

Regarding the assessment of carbohydrate metabolism impairment using IVGTT data, the D2-index can be utilized to evaluate the appropriateness of transitioning a patient with DM2 from non-insulin antidiabetic drugs to insulin therapy: the higher its positive value, the more appropriate insulin therapy becomes, while the lower its negative value, the more justified the use of non-insulin antidiabetic drugs.

From the above, it is evident that the developed method for diagnosing DM based on IVGTT results introduces new approaches to selecting and evaluating the effectiveness of antidiabetic therapy, some of which have been outlined above.
In conclusion, we present two clinical examples demonstrating how the newly developed method for analyzing IVGTT data can be applied in routine clinical practice.

Case 1

Patient Nc., 55 years old, without DM, body mass index (BMI) 27.5 kg/m². The patient is receiving gliflozin to reduce body weight. An IVGTT was performed, and the position of the calculated two-dimensional glucose kinetics parameter P(K,D) is shown in Figure 2. The glucose kinetics parameters in IVGTT are as follows:

- Fasting glucose: 5.1 mmol/L
- K-index: 8.2 (normal range: 1.7–3.8) mmol/L/min
- H-index: 4.5 (normal range: 0.0–5.4) mmol/L
- D1-index: -5.6 (normal range: -0.09 to -1.8)

*Conclusion***.** According to IVGTT data, the patient does not have DM: the D1-index is -5.6, meaning the two-dimensional glucose kinetics parameter, point P(K,D), is located below the D1 curve. DM is also not detected using other traditional diagnostic tests. However, the observed very high glucose elimination rate (K-index is nearly twice the upper limit of the normal range) reflects the effect of gliflozin, which removes a significant portion of glucose from the blood via urine. This outcome aligns with the purpose of taking gliflozin, as the patient aims to reduce her current body weight.

Case 2

Patient Kz., 42 years old, without DM (HbA1c 5%, indicating normal levels; OGTT results are also within normal limits), BMI 24.6 kg/m². An IVGTT was performed, and the position of the calculated two-dimensional glucose kinetics parameter P(K,D) is shown in Figure 2. The glucose kinetics parameters in IVGTT are as follows (values in parentheses represent the 5th–95th percentiles of reference ranges for all parameters except fasting glucose):

- Fasting glucose: 4.8 mmol/L
- K-index: 1.5 mmol/L/min
- H-index: 4.8 (reference range: 1.7–3.8) mmol/L
- D1-index: -0.54 (reference range: -0.09 to -1.8)
- D2-index: -0.99 (reference range: -0.17 to -1.48)

***Conclusion*.** The patient was found to have impairments in glucose kinetics parameters during IVGTT without signs of hyperglycemia (i.e., no DM). According to modern classification, this corresponds to "prediabetes" or what can be termed "metabolic DM," meaning non-hyperglycemic (subclinical) DM.

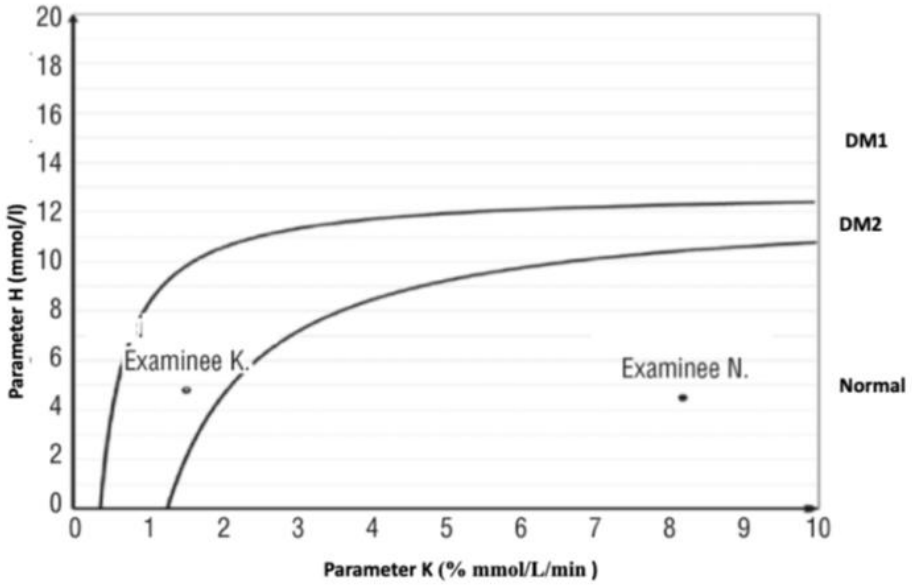

Figure 2: Two-dimensional parameters of glucose kinetics P(K,D) in the subjects N. and K.

If the IVGTT parameters of Kz. are compared with those of Nc. from the first example (treated with gliflozin), it becomes apparent that if the effect of gliflozin administration in Kz. is similar to that observed in Nc., the two-dimensional parameter P(K,D) for Kz. would shift to the right on Graph 2, reaching the level observed in Nc., i.e., within the normal range of the K-index. Since hepatic glucose production in Kz. is normal, this would result in the normalization of both K-index and H-index glucose kinetics parameters.

Discussion

The developed method for processing IVGTT data allows not only for the clear distinction between individuals with and without DM but also for the assessment of the severity of carbohydrate metabolism impairment. Additionally, it enables the detection of DM at the stage of glucose kinetics disturbances, i.e., before these disturbances lead to the development of hyperglycemia. Since the method separately monitors hepatic glucose production and its elimination, it opens new possibilities for selecting antidiabetic drugs and evaluating their effectiveness, particularly based on which glucose kinetics parameters are altered and to what extent.

Based on the above, indications for performing IVGTT can be formulated as follows:

- **For individuals at high risk of developing DM2**: To identify DM at the prediabetic stage, i.e., during glucose kinetics disturbances before the hyperglycemic stage develops. This would allow for the prescription of pharmacotherapy tailored to correct the detected glucose kinetics imbalance, depending on the specific disturbances, and prevent the progression from prediabetes ("metabolic DM") to overt DM.
- **For newly diagnosed DM2**: To determine the nature of hepatic glucose production and elimination impairments and select the optimal initial non-insulin antidiabetic therapy—whether targeting hepatic glucose production, glucose elimination, or both simultaneously.
- **For long-term DM2 treatment with non-insulin antidiabetic drugs**: To evaluate the severity of glucose kinetics impairments and determine whether the impairment has reached a stage warranting insulin therapy.
- **For DM1**: To identify excessive hepatic glucose production uncorrected by insulin therapy, thereby justifying the addition of a drug that addresses hyperglucagonemia (e.g., GLP-1 receptor agonists), and consequently reduces hepatic glucose overproduction.

Conclusions

1. The developed method for processing IVGTT data allows for the clear differentiation between individuals with and without DM, as well as for the assessment of the severity of carbohydrate metabolism impairment. It also enables the detection of DM at the stage of glucose kinetics disturbances, i.e., before these disturbances lead to the development of hyperglycemia.
2. The IVGTT data analysis method allows for separate monitoring of hepatic glucose production and its elimination from the blood in individuals, opening new possibilities for selecting antidiabetic drugs and evaluating their effectiveness. Specifically, treatment regimens for DM have been proposed based on the four identified variants of glucose kinetics in IVGTT.
3. Two clinical examples demonstrate how prescribed antidiabetic drugs influence glucose elimination rates in IVGTT and how glucose kinetics disturbances manifest before the development of hyperglycemia.

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