Research Article

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IVGTT in Diagnosing of Glucose Kinetics Dis-balance in Diabetic Patients

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Currently, there are two approaches that are used during the clinical diagnostics of diabetes: (a) according to the results of a static study of glycemia (in a fasting state and/or at a random point within 24 hours), and diabetes is diagnosed when the glycemia level exceeds a certain threshold value; (b) using a dynamic stress test, or OGTT (2 hours after taking 75g glucose), which also sets threshold values for normal glycemia at the 2-hour test point. But as early as 1943, another dynamic method for diagnosing diabetes, IVGTT (Greville), was proposed, in addition to OGTT. The advantages of the IVGTT method over the OGTT method in the accuracy of diagnosing diabetes are obvious. First of all, this is due to the fact that insulin has no influence on the absorption of glucose, but only on the rate of glucose elimination from blood. And, in the OGTT, not only the elimination of glucose from blood is reflected, but also the processes of glucose absorption from the gastrointestinal tract, which have nothing to do with insulin deficiency. On this basis, in 1943, Greville suggested using IVGTT for diagnosing diabetes and, as stated in this study, was quite successful. Moreover, to calculate the rate of glucose elimination from the blood, Greville proposed a simple kinetic model where the rate of glucose decreases in blood ($dC(t)/dt$) after an intravenous bolus injection (approximately 20g, IV push for a few minutes) was considered proportional to the concentration of blood glucose (C) with a proportionality factor of k:

$$dC(t)/dt = -k*C(t) \quad (1)$$

It is clear that the higher the k factor, the higher the rate of glucose reduction in blood, and therefore, its value can be used as an indicator of the degree of impairment of glucose utilization from blood.

With that in mind, in diabetes mellitus, the lower the k factor is, the more pronounced the insulin deficiency will be, and therefore, it could be a rather simple and objective criterion for diagnosing diabetes.

However, when attempting to introduce this method of diagnosing diabetes, one technical problem arose, which Greville had already focused on in his first study. Let's omit the mathematical details justifying the necessity of calculating the k factor based on the semi-logarithmic graph presented in Figure 1. The point of the calculation is to determine the inclination of the line of glycemia logarithms ($lnC(t)$) to the abscissa axis (time t in the test) — this is essentially the k factor. And the $lnC(t)$ points must fall along the line on the graph. Unfortunately, as Greville noted, with regards to these points of the glycemia logarithm, the more they deviate upwards from the line, the further the glycemia moves away from the beginning of the test (Figure 1).

As a result, it was impossible to definitely determine the factor, and, moreover, if we ignore this systematic deviation and draw a direct regression line through the glycemic logarithm points, some patients with clinical findings of diabetes mellitus will have a normal k factor.

Greville's proposal to improve the method of calculating the k factor by taking the logarithm of the difference between glycemia in the test (G(t)) and fasting glycemia (FBG) gives even worse results — the $ln(G(t) — FBG)$ points in semi-logarithmic coordinates still systematically deviate downwards from the line at the end of the

graph, and to an even greater extent than upwards ln G(t) (Figure 1). As a result, it was impossible to unambiguously calculate the k value through this approach. No explanation was given to this phenomenon and they opted to simplify the test — only the initial 20 minutes of the test were included in the k factor calculation, where the location of ln G(t) points was more or less in a straight line. Owing to the methodological problems, the "truncated" IVGTT method has been used only in scientific research and abandoned in clinical practice until now.
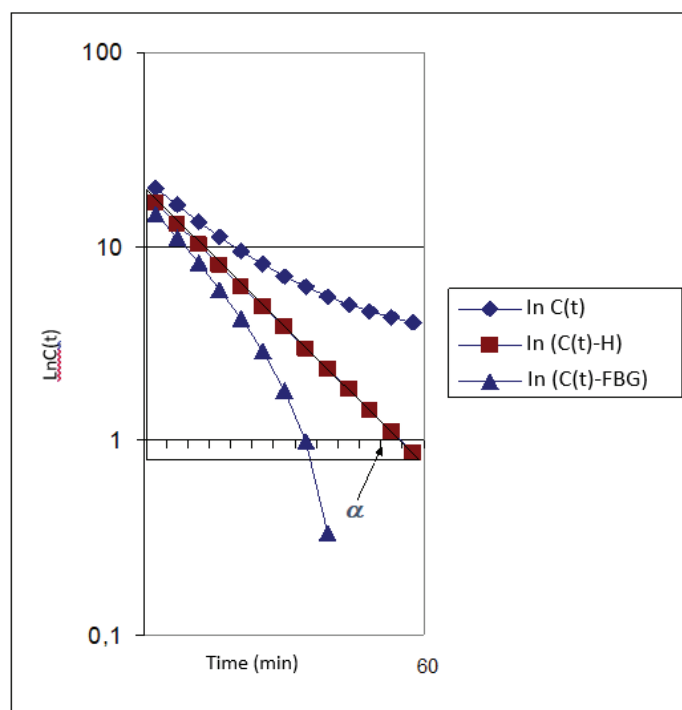

Figure 1: *The behavior pattern in the semi-logarithmic coordinates of glycemia data (C(t)), the difference in glycemia and fasting blood glucose (C(t)-FBG), as well as glycemia and the calculated indicator H (C(t)-H).*

In the 80s, a hypothesis (2,3) was proposed to explain the observed phenomenon and, based thereon, the method for calculating the k-criterion was corrected, which allowed not only for the unambiguous separation of patients with diabetes from healthy ones, but according to the results of IVGTT, also patients with type 1 diabetes from those with type 2 diabetes, as well as early carbohydrate metabolism disorders from overt diabetes (Figure 2).

However, it was even possible to get an indirect assessment of liver glucose production. But unfortunately, this could not save IVGTT from neglect, and OGTT still continues to be used as the only dynamic test for diagnosing diabetes recognized by diabetologists.

Nevertheless, the improved method for diagnosing diabetes according to the IVGTT results may be revived, for example, because antihyperglycemic drugs have been devised in recent years that influence the production of liver glucose (incretin series, in particular), and identifying among patients with diabetes those with predominantly impaired liver glucose production, compared to its glucose elimination, can only be made via the adjusted method of processing the IVGTT results. Let us consider below the principle of adjusted IVGTT and specify the advantages it gives in comparison with the traditional OGTT method.

Generally speaking, the simplest glucose kinetic model (1) works quite efficiently in hepatectomized rats, i.e. in cases of rats without a liver, the logarithmic points lnC(t) of IVGTT glycemia for calculating the k factor fall exactly along the straight regression line and no systematic deviations are observed. It follows as a logical consequence that the observed systematic deviation from the line of lnG(t) points is due to the fact that liver glucose production is preserved in the IVGTT process and it should be taken into account in the glucose kinetic model. Conceptually, this is simple: we assume that the rate of glucose elimination from the blood (dG(t)/dt) is proportional not to the glycemia level in the test G(t), but to the difference between glycemia created by intravenous glucose in the test and the concentration of blood glucose, which depends on the liver glucose production (H), and let's assume for simplicity, that this production can be considered an average for the test, i.e. constant. That is, H, like k, is an unknown constant, which must be determined according to the test results. In simpler terms, the mathematical model of glucose kinetics in the test will be as follows:

$$dG(t)/dt = k*(C(t) – H) \quad (2)$$

Thus, a mathematical problem arises: how is it possible to calculate not only k, but also H from the IVGTT results? Various mathematical solutions are possible, however, physiologically, the most obvious solution was actually suggested in studies published in the 80s in Russian scientific literature (2,3), and later issued in English as well (4).

The principle of the method is based on the fact that in hepatecto-mized rats the lnG(t) points do not deviate from the straight line in the coordinates of Figure 1, that is, a simple model (1) adequately describes the glucose kinetics, if the influence of the liver (indicator H) is eliminated. It is obvious that liver glucose production in the test is lower than the fasting value, but at the same time it may well not be zero. Consequently, the H value falls somewhere between 0 to fasting glycemia FBG. Hence, if we choose in the range of 0 to FBG values such an H number to place the lnG(t)-H test points as close as possible to the straight line on the graph (Ln(G(t)-H, t,) (Fig. 1) (in fact, the minimum distance of the lnG(t)-H points to the regression line drawn through these points in the coordinates of Figure 1 is sought), it will reflect the average concentration of blood glucose H, produced by the liver in the course of IVGTT. If this mathematical process is described biologically, it is assumed that the simplest model of glucose kinetics (1) adequately reflects the glucose kinetics in the test, and the systematic distortion of its results (deviation from the straight line upwards of the LnC(t) points) shows the influence of the liver (production of liver glucose in the test), since there is no other glucose source complementary to the test but the liver in IVGTT. Therefore, if the observed distortion is eliminated (the curve is straightened), the degree of straight line distortion is an indirect indicator of liver glucose production, i.e. indicator H.

If this hypothesis is true, then the proposed approach should make it possible to unambiguously diagnose diabetes mellitus using IVGTT, including all points of the test, and not truncating them to the first 20 minutes, when liver glucose production must be suppressed (zero or close to zero). In contrast to the simplest glucose kinetics model (1), model (2) can provide not only the k indicator (glucose elimination rate), but also the H indicator, indirectly reflecting the liver glucose production. Consequently, the profiles of carbohydrate metabolism in a patient being studied should be represented on a two-dimensional graph (k,H) by a point (two-dimensional indicator) P(k,H).

The results of calculating the P(k,H) indicators in patients without diabetes and with type 1 and type 2 diabetes are shown in Figure 2, where the location of P(k,H) points (indicators) clearly differs not only between healthy and diabetic patients, but also between patients with type 1 and type 2 diabetes. Between these areas, 2 discriminant curves D(t) can be made to provide the threshold criteria in diagnosing diabetes, in particular, the distance from P(k,H) to the discriminant curve separating diabetic patients from the healthy

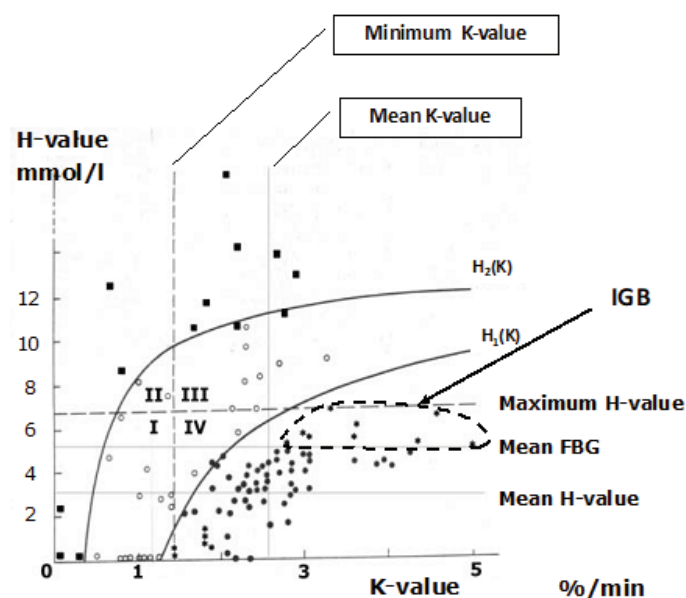can be used as an indicator of the degree of carbohydrate metabolism disorder.

Figure 2: The bi dimensional P(K,H) index of glucose kinetics in non-diabetics and diabetics. In the figure are pointed out minimum K-value, mean K-value, maximum H-value, mean FBG and mean H-value of non-diabetics. IGB – impaired glucose balance. $H_1(K)$ and $H_2(K)$ – discriminant functions. I-IV - four distinguishable variants of the glucose dis balance in overt diabetes mellitus

● - P(K,H) indexes of non-diabetics; ○ - P (K,H) indexes of type 2 diabetics ("mild" metabolic disturbances);

■ - P(K,H) indexes of type 1 diabetics ("severe" metabolic disturbances)

It can also be seen from Figure 2 that in some patients, the carbohydrate metabolism disorder is associated not with an impaired glucose elimination (they have a normal k value), but with increased liver glucose production (increased H indicator) or vice versa. Considering all the aspects of the pathological combination of k and H indicators, the 2 types of diabetes currently distinguished fall into 7 subtypes (Table 1). That is, the proposed method for the IVGTT analysis, in contrast to the used OGTT, allows for the assessment of the carbohydrate metabolism disorder in diabetes mellitus not in a static condition (blood glucose level), but in a dynamic state (through the glucose flow into blood from the liver (H) and from blood to tissue (k)), which enables the distinguishing of its new subtypes and, therefore, new treatment prospects to correct not only the blood glucose level, but also the intensity of glucose flows.

In particular, Figure 2 also shows that among the patients without impaired carbohydrate metabolism, those with a very high production of blood glucose (H) are clearly distinguished, which is compensated by its high elimination (k) and, therefore, hyperglycemia does not develop. On the other hand, there are patients with a very low elimination of blood glucose (k), which is compensated by very low liver glucose production (H), otherwise these patients developed hyperglycemia (i.e. diabetes). This data allows for substance to be given to a currently vague and abstract "prediabetes" term: "prediabetes" should include conditions where glycemia is normal, but glucose kinetics (produced by the liver/elimination from blood) is disturbed, which at this stage of the disease, although pathological, is balanced in a way that does not lead to hyperglycemia.

It is clear that a practical disadvantage of BTTG is the complexity of the glycemic examination procedure, first of all, the need for frequent examination of glycemia in the venous blood. However, on the basis of the method of continuous glycemic research already used in the clinic, it is easy to develop a method for diagnosing diabetes based on the intravenous injection of blood glucose that is not burdensome for clinical practice. Ultimately, if IVGTT allows for the diagnosis of carbohydrate metabolism disorders that cannot be detected by any other method and are significant for choosing the optimal treatment of diabetes, then the indicated technical difficulties of the procedure can be justified.

Thus, in actual fact, the described method for the IVGTT analysis allows for the proposal of a new paradigm of pathogenesis, respectively, of the diagnosis and treatment of diabetes mellitus — considering this disease not only in terms of impaired blood glucose homeostasis (that is, maintaining blood glucose levels in a given range), but also the regulation of glucose flows, where glycemia homeostasis is a derivative, secondary to the regulation of glucose flows. In terms of this paradigm, the mechanisms and methods for treating diabetes can be reviewed. Generally speaking, considering diabetes within the new paradigm would be pointless for practical diabetology if there were no method, albeit indirect, for assessing glucose flows. Since the method for assessing a patient's glucose flows is presented above and its efficiency has actually been confirmed in normal clinical practice, I believe it is time in diabetology to lean toward this new direction.

A more detailed mathematical justification of the proposed method for processing the IVGTT results can be found in the article (4). Here we only note that the increasing deviation of the lnC(t) points from the line to the end of the test is not associated with the restoration of glucose production by the liver in the test, as one might assume, but with a purely mathematical miscalculation.

Types of diabetes	Variant of glucose disbalance			
	I (H norm, K↓)	II (H↑, K↓)	III (H↑, K norm)	IV (H norm, K norm, but P(K,H) is beyond H1(K))
DM1	1-I (23%)	1-II (15%)	1-III (62%)	-
DM2	2-I (63%)	2-II (7%)	2-III (30%)	2-IV (7%)

Table 1: *Seven subtypes of diabetes mellitus are distinguished when type 2 and type 1 of DM are overlaid on four variants of glucose dis balance, revealed in IVGTT.*

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