On a Mathematical Model for the Analysis of the Glucose Tolerance Curve

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SUMMARY

Three hundred and seventeen oral glucose tolerance curves have been analyzed by a mathematical model (Ackerman's model).

By application of the model to continuous venous infusion the validity of the Ackerman's hypothesis on the glucose intestinal absorption has been confirmed. The results demonstrated that the intestinal absorption rate of glucose was not statistically changed in diabetes mellitus, but decreased with age.

The period of curve T, which characterizes the glucose-insulin feed-back, the glucose fasting level and the coefficient α, which characterizes insulin removal rate independent of blood glucose and the decrease of blood glucose independent of insulin, resulted in significant differences between normal and diabetic subjects. The error involved in this method was about 7.5 per cent. DIABETES *19*:445-49, June, 1970.

In 1964 Ackerman and colleagues[1,2] proposed a mathematical model of the glucose-insulin system which gives a more reliable valuation of the glucose-tolerance curve for diagnostic purposes than the morphological or semiquantitative criteria employed at present.

This model, which constitutes a rough approximation of reality, characterizes the system with six constants $I_1 \ldots I_6$. For the significance of these constants we refer to the work of Ackerman et al.[1] The constants give rise to the differential equations:

$$\dot{G}(t) = -I_4 G(t) + I_5 - I_6 H(t) + I(t)$$

$$\dot{H}(t) = -I_1 H(t) + I_2 + I_3 G(t).$$

These equations bind the blood-glucose $G(t)$ and insulin $H(t)$ concentrations to their derivatives, and $I(t)$ is a function which represents the intake rate of glucose into the bloodstream.

If G_F and H_F are the fasting values of these two variables, and $g(t) = G(t) - G_F$, and $h(t) = H(t) - H_F$, the two differential equations give rise to the following second order equation:

$$\ddot{g}(t) + (I_1+I_4)\,\dot{g}(t) + (I_1I_4+I_3I_6)\,g(t) = I_1 I(t) + \dot{I}(t) \quad (1)$$

In the glucose-tolerance test, $I(t)$ evidently represents the intestinal absorption rate. Ackerman et al. have introduced the hypothesis that the term $I_1 I(t)$ is negligible in comparison to $\dot{I}(t)$ and that the latter may be expressed as the product of a constant B for the function of Dirac $\delta(t)$. The constant B thus assumes the signification of the relation between the intake rate (mg./min.) and the total volume of the glucose compartment expressed by units of 100 ml.

Equation (1) can therefore be written:

$$\ddot{g}(t) + (I_1+I_4)\,\dot{g}(t) + (I_1I_4+I_3I_6)\,g(t) = B\delta(t)$$

Putting $\frac{I_1 + I_4}{2} = \alpha$ and $I_1 I_4 + I_3 I_6 = \omega_0^2$,

the previous equation has the following solutions:

$$g_1(t) = \frac{B}{\omega} e^{-\alpha t} \sin \omega t \qquad \text{for } \omega_0^2 > \alpha^2 \quad (2)$$

where $\omega = \sqrt{\omega_0^2 - \alpha^2}$

$$g_2(t) = \frac{B}{2\omega} e^{-\alpha t} (e^{\omega t} - e^{-\omega t}) \qquad \text{for } \omega_0^2 < \alpha^2 \quad (3)$$

where $\omega = \sqrt{\alpha^2 - \omega_0^2}$.

These correspond to the oscillatory or aperiodic glucose-tolerance curves.

By a best-fitting method it is possible for each glucose-tolerance curve to determine the parameters B, α and ω_0^2 which characterize it. In an analysis of this type, Ackerman found (a) that the glucose tolerance curves are actually type 2 or 3 whether they relate to normal or diabetic subjects; (b) that the parameter which distinguishes best between the curves of normal and diabetic subjects is ω_0 or the equivalent appropriate period $T = 2\pi/\omega_0$ in the sense that for normal subjects T is small, while for diabetics it is large. The

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best limit value for the distinction is according to Ackerman, T = 240 minutes.

The purpose of the present study was to verify these results because of practical application. In addition, we directed attention further than the period T to the other constants α, G_F and B which characterize the glucose-tolerance curve and which have not been considered as discriminating parameters by Ackerman.

Before beginning this verification we wanted to control the validity of Ackerman's hypothesis concerning intestinal absorption, on the basis of the following considerations:

A detailed analysis shows that the hypothesis of Ackerman et al. is justified when one supposes that the constant I_1 (average relative rate of insulin removal independent of glucose) is small compared to ω_0 which represents the resonant frequency peculiar to the system.

Since the condition $I_1 << \omega_0$ is evidently a characteristic of the system and therefore independent from the form of the I (t), it is clear that the solution reached by Ackerman et al. for the glucose-tolerance test is also applicable to the continuous venous infusion curve which does not differ from the former. In fact, for continuous venous infusion at a steady rate which begins at the time t = o, we have I (t) = o for t < o and I (t) = B for t $\geq$ o, i.e. I(t) is a step-function of the time; $\dot{I}$ (t) may thus be expressed as B δ (t) and therefore eliminating I_1 B, one still obtains Ackerman's equation for the glucose-tolerance test.

These considerations allow a direct verification of the value of Ackerman's hypothesis with regard to intestinal absorption.

A simulation study of the intestinal glucose absorption has been carried out by Gatewood et al.[3,4]

Verification of the Ackerman hypothesis with regard to intestinal absorption

If we have a continuous venous infusion curve with v rate expressed in grams/hour, the corresponding value of B expressed in mg./min. 100 ml. is

$$B = 1.67 \frac{v}{V} \qquad (4)$$

where V is the volume of the glucose pool expressed in liters. The constant 1.67 is a factor dependent on the chosen units of measurement with the units given above:

$$B\ (\text{mg./min. 100 ml.}) = \frac{v\ (g/h) \cdot \frac{10^3}{60}}{V\ (\text{lit.}) \cdot 10} = \frac{v\ (g/h)}{V\ (\text{lit.})} \cdot 1.67$$

For this purpose we used the continuous venous infusion experimental curves published by Moorhouse[5] and by the best-fitting method we determined the values of B corresponding to the various rates of infusion which the author indicated. The results are reproduced in table 1 and in figure 1.

TABLE 1

v(g/h)	B(mg./min. 100 ml.)	V(liters)	
8	1.734	7.70	Normal
30	3.829	13.08	kg. 76
65	10.393	10.44	$V_0 = 11.4$
12	2.117	9.47	Diabetic
16	2,686	9.95	kg. 67
26	2.122	22.03	$V_0 = 10.0$

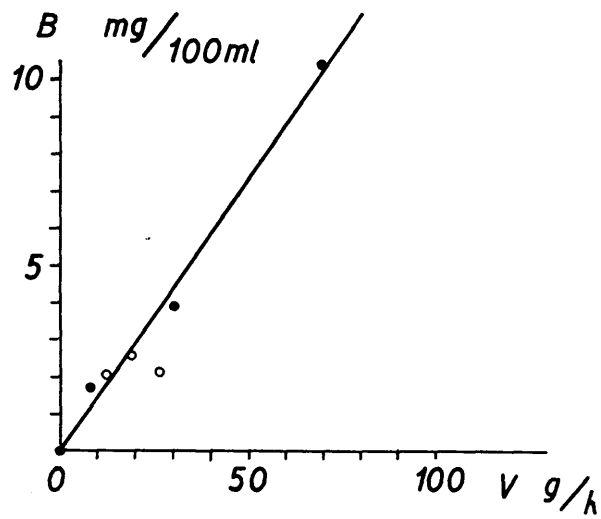

FIG. 1. Values of B calculated from continuous infusion curves as a function of the rate of infusion v.

Once the value of B has been calculated for each curve, the corresponding value of v being known, it is possible to estimate the value of V by (4).

As seen in the table, the values of V thus estimated are in accordance with the value of the volume V_0 of extracellular fluid whose weight may be valued approximately at 15 per cent of the body weight.[6] The difference of the last point may be attributed to the urinary elimination of glucose. This accordance indicates that the intestinal absorption scheme introduced by Ackerman's model must be considered essentially correct.

MATERIAL AND METHODS

Three hundred and seventeen glucose-tolerance curves have been used, obtained by administering 1 gm. of glucose per kilo of body weight orally in a single

dose, and by determining the blood glucose level on the AutoAnalyzer by the Hoffman method.[7] Blood samples were drawn every thirty minutes over a period of three hours. The subjects were of approximately equal sex distribution, ages twenty to eighty-nine.

Each curve was related to the normal or diabetic subject in regard to the following variables:

a. Familial history of diabetes.

b. Postprandial blood glucose level and glycosuria.

c. Clinical examination of the eye.

d. Glucose-tolerance curve accompanied, for uncertain cases, by the tolbutamide test.

e. Levels of total serum cholesterol, ratio of β/α lipoproteins, and the levels of uric acid.

Values of the glucose-tolerance tests were judged abnormal as follows:

1. > 200 mg./100 ml. at the first hour.
2. > 140 mg./100 ml. at the second hour.
3. > fasting level + 30 mg./ml. at the third hour.

If none of these criteria was met, the subject was judged normal. If all three criteria were met, the subject was judged diabetic. In this way seventy-five normal and sixty-one diabetic subjects were selected from all the cases examined.

The characteristic parameters G_F, T_0, α and B were obtained from each experimental curve by a best-fitting method with the expressions (2) or (3). The fitting procedure consists in a least square method minimizing the sum of the squares of the deviations of the experimental points from the calculated curve. The calculation, made by means of an IBM 1620 computer, does not take more than ten seconds.

Correlation of the curve parameters with diabetes

In keeping with the model, damped oscillatory and aperiodic curves were looked for. The percentage of aperiodic curves was 18 per cent in normal subjects and 20 per cent in diabetics. Accordingly, there was no evidence for the aperiodicity of the glucose-tolerance curve in diabetes.

In 13 per cent of the cases it was impossible to approximate the experimental curves with (2) and (3)-type expressions. In nearly all these cases we observed that the experimental curves present two peaks and are therefore of the type described by Azerard and Duprey.[8] These abnormal curves have been excluded from the statistics. They were more or less equally distributed between normal and diabetic subjects.

The oscillatory and aperiodic curves were separated from each other because statistical analysis of the values of the parameters T, α, G_F and B showed that the corresponding average values were significantly different in the two groups of curves. It was therefore logical to look at these as related to two different populations. The reason for the existence of these two populations is not known. There did not seem to be any link either with diabetes or with the age of the subject.

The average values of the parameters and their standard deviations for the normal and diabetic subjects are reproduced in table 2. The third column indicates the significance level of the difference between the average values.

TABLE 2

	Normals (61)	Diabetics (47)	Significance of the difference (Student *t* test)
Oscillatory curves			
B	5.074±0.51	4.684±0.27	no sign
T	198.2±5.8	340.8±10.7	0.5%
α	0.0202±0.0015	0.00953±0.0010	0.5%
G_F	101.1±1.6	129.2±4.2	0.5%
Aperiodic curves			
	Normals (14)	Diabetics (13)	
B	10.34±2.76	6.30±0.76	no sign
T	169.6±7.9	382.3±30.2	0.5%
α	0.054±0.0080	0.022±0.0013	0.5%
G_F	94.0±3.3	121.2±11.9	2.5%

The values of α, T and G_F for normal subject are in good agreement with the values obtained by Ceresa et al.[9] in the analysis of intravenous infusion of glucose curves with a more elaborate mathematical model.[9,10]

As one can see, the rate of intestinal absorption B is not significantly different between normal and diabetic subjects, while all the other parameters have a significant difference; so each of these can, potentially, give information about the presence or absence of diabetes.

The fasting blood glucose level G_F, reproduced in the table, is the value calculated by the best-fitting method which is generally slightly superior to that directly measured, as may be expected with the type of approximation introduced into the model.

With regard to the coefficient α there is a sensitive difference between normal and diabetic subjects, and a systematically inferior value specifically in the latter. It is interesting to note that this difference exists notwithstanding the fact that the constant α does not contain the parameters which characterize the glucose-insulin

feedback (I_3 and I_6), but is bound to the insulin removal rate independent of glucose (I_1) and to that of glucose independent of insulin (I_4). It seems therefore that these rates are generally lower in diabetic than in normal subjects.

Correlation of the glucose-tolerance curve parameters with age

It is well known that the morphological characteristics of the glucose-tolerance curve depend, to a certain extent, on the age of the subject.[11,19] Since we are dealing with a group of subjects whose ages range between twenty and eighty-nine years, we have considered it interesting to find out whether the single parameters characteristic of the glucose-tolerance curve depend on age.

This research was carried out on definitely normal subjects in order to separate the parametrical changes correlated to age from those correlated to diabetes. Only the oscillatory curves were examined because there are too few aperiodic curves to give a statistically significant result. With regard to the parameter B which characterizes the rate of intestinal absorption, since we have shown that this is not significantly different between normal and diabetic subjects, we investigated all the available data. As a result we found that the parameter B diminishes significantly with age ($p < 0.05$). Taking a linear correlation we calculated the parameters of the straight line $B = -0.027\ E + 6.359$ where E is the age of the subject in years. The existence of this correlation is interesting because a value of B, different for older and younger subjects, can make modifications of the glucose-tolerance curve, which may distort a judgement based uniquely on the morphology of the curve.

Whether in the oscillatory or the aperiodic curves, the parameters G_F and α do not present a significant correlation with age.

Analyzing the values of the period T, a significant correlation ($p < 0.05$) emerges in the augmentation of the period with age:

$$T = 0.836\ E + 150.7$$

where with E we indicate age in years.

Analyses of the glucose-tolerance curve. Discriminating functions.

As we have seen, the characteristic parameters of the glucose-tolerance curves present, with the exception of the intestinal absorption rate of glucose, more or less important differences between normal and diabetic subjects.

In this case the best way to use the data of the glucose-tolerance curve for diagnostic purposes is to single out a unique parameter, that is, a function of G_F, T and α, which presents the greatest possibility of discrimination. This may be obtained by constructing the discrimination function

$$L = \lambda_{G_F}\ G_F + \lambda_{\ T} T + \lambda_{\ \alpha} \alpha$$

whose coefficients λ_{G_F}, λ_T and $\lambda\alpha$ are determinable by the discriminatory statistics analyses method.

In this way each glucose-tolerance curve is characterized by the unique parameter L and is ascribed to a normal or diabetic subject, whether L turns out to be smaller or greater than a prefixed value L_o. This latter is statistically determinable in such a way as to have maximum discriminatory efficiency, taking into account the statistical fluctuation of single parameters.

In this calculation, which was carried out for the oscillatory curves, it is possible to keep an account of the dependency of T on age, relating its value to the standard age of thirty-five years by means of the straight line of regression indicated above.

By our experimental data we find that the coefficients and the discrimination limit L_o have the following values:

Parameters		Contribute to the discrimination
λ_T =	0.462	78%
$\lambda\alpha$ =	54	1%
λ_{G_F} =	0.622	21%
L_o =	175.8	

In figure 2 the values of L for definitely normal and definitely diabetic subjects have been reproduced in a histogram, calculated by the values of λ indicated above.

It is possible to evaluate the statistical error in the discrimination carried out by means of the parameter L. The error committed in the discrimination from our

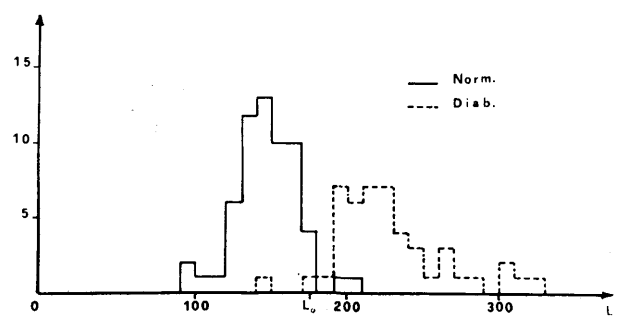

FIG. 2. Distribution of L values for definitely normal (—) and definitely diabetic (----) subjects.

data is of about 7.5 per cent.

Analyzing, by this method, all the glucose-tolerance curves available, one notices a disagreement with the medical diagnosis of 15 per cent of the cases. This amount is substantially acceptable in as much as 7.5 per cent is the inherent error of the method, and it is reasonable to attribute the remaining 7.5 per cent to an erroneous medical diagnosis, if one takes into account the numerous cases in which this diagnosis is anything but certain.

Subsequently valuing the three semiquantitative criteria now used to analyze the glucose-tolerance curve, one notices that the average error linked to each of these is as follows:

Blood glucose $>$ 200 mg./100 ml. at the first hour:
errors 51 per cent.

Blood glucose $>$ 140 mg./100 ml. at the second hour:
errors 30 per cent.

Blood glucose $>$ fasting level + 30 mg./100 ml. at the third hour:
errors 47 per cent.

CONCLUSION

By what we have stated, we can safely say that Ackerman model of the glucose-tolerance curve, although representing a rough outline, provides a substantially correct interpretation of the glucose-tolerance curve.

By analyzing the results obtained studying 272 glucose-tolerance curves, we have been able to determine that the intestinal rate of absorption is not significantly different between normal and diabetic subjects, but depends on age in the sense that it diminishes with age.

Since either the period T, the base level G_F and the coefficient α are significantly different between normal and diabetic subjects, the best information obtainable from a glucose-tolerance curve is given by the discriminating function L.

As the determination of L, starting with the experimental data carried out by a computer, does not take longer than about ten seconds, we maintain that its systematic use could establish an element of notable importance in the diagnosis of diabetes.

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