Glucose Tolerance and Insulin Release, A Mathematical Approach

I. Assay of the Beta-cell Response After Oral Glucose Loading

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SUMMARY

From the dose-response relations between glucose and insulin after oral glucose loading, a reproducible parameter for beta-cell response was deduced. The main advantage of this parameter —corrected insulin response, defined as CIR = I·100/G(G−70)— lies in its independence from the initial or reached glucose level. DIABETES *25*:241-44, April, 1976.

The usual criteria for the beta-cell response after oral glucose loading are—the absolute insulin level reached at different intervals; the ratio of the insulin level and the glucose level; the insulinogenic index[1] (the ratio of the insulin increment and the glucose increment); any kind of summation or integration of these parameters.

However, glucose and insulin curves may vary markedly even in the same subject tested under identical circumstances. Furthermore the dose-response curve of insulin to glucose is not a straight line but an exponential one.[2] In other words, a fixed glucose increment will elicit a greater insulin response when starting from a higher glucose level (figure 1). With changes of pancreatic beta-cell function this curve shifts to the right or the left but does not lose its nonlinear form.[3] From this relation it can readily be deduced that the rather empirically chosen parameters I, I/G, and $\Delta I/\Delta G$ will be a function of the glucose level. We are, however, in search of a parameter of insulin secretion that gives information about pancreatic function independently of the glucose level reached. Therefore we tried to approximate mathematically the insulin-glucose relationship for glucose values during an oral GTT and from this relation to deduce a glucose-independent judgment of the insulin response and to test its reproducibility.

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METHODS

An oral GTT with 100 gm. of glucose after three days of a carbohydrate-rich diet was performed in 14 men of normal weight without a family history of diabetes. The test was repeated with an interval of at least two days under identical circumstances in 10 individuals. These individuals were not selected on the basis of age, weight, or diabetic history.

Glucose was measured by a ferricyanide method on an AutoAnalyzer in whole venous blood and insulin by a double-antibody radioimmunoassay.

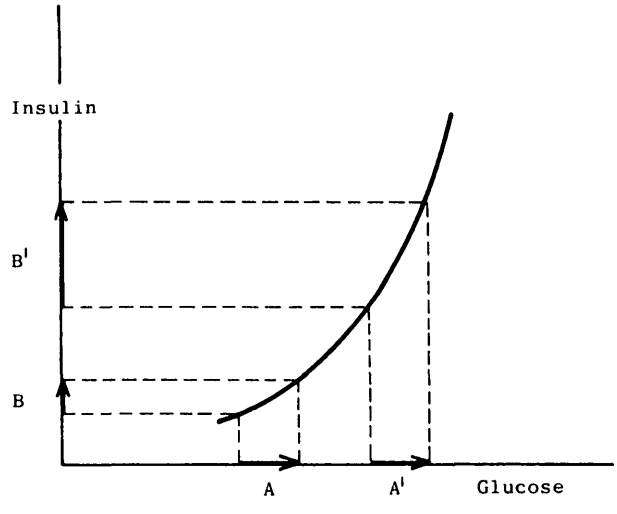

FIG. 1. Schematic dose-response curve of insulin and glucose after oral glucose loading. A fixed glucose increment (A) will give a smaller insulin increment (B) when starting from a low glucose level than the same increment (A') starting from a high glucose level (B') (derived from the article of Cerasi et al.[2]).

TABLE 1

Glucose and insulin values and ratios after oral glucose loading in 14 normal men. CIR deduction is described in the text

Subject	G (mg./100 ml.)				I (μU./ml.)				I/G			CIR		
no.	0	10	20	30	0	10	20	30	10	20	30	10	20	30
1	74	82	98	96	8	16	45	42	0.195	0.462	0.483	1.62	1.63	
2	74	104	116	108	12	43	70	62	0.413	0.606	0.571	1.21	1.31	
3	81	99	118	118	10	19	40	55	0.192	0.339	0.446	0.66	0.70	
4	63	89	102	88	12	39	105	45	0.483	1.024	0.512	2.30	3.21	
5	82	93	116	131	5	29	38	57	0.312	0.328	0.435	1.35	0.71	0.71
6	80	102	122	130	14	67	87	115	0.656	0.713	0.885	2.05	1.37	1.77
7	74	97	104	96	6	25	35	33	0.258	0.338	0.344	0.96	0.99	
8	82	86	110	130	11	25	47	70	0.291	0.427	0.441	1.81	1.06	0.89
9	92	106	129	148	8	18	45	58	0.170	0.349	0.392	0.47	0.59	0.50
10	72	94	120	130	6	34	55	45	0.361	0.458	0.364	1.50	0.91	0.57
11	72	94	115	120	3	28	85	72	0.298	0.739	0.652	1.24	1.63	1.64
12	84	94	110	124	8	45	90	90	0.479	0.776	0.726	1.99	1.68	1.34
13	78	98	122	126	10	28	80	75	0.286	0.656	0.595	1.02	1.26	1.06
14	89	119	148	150	8	90	220	180	0.756	1.486	1.200	1.54	1.90	1.50

Deduction of a Glucose-independent Parameter of Beta-cell Function, the Corrected Insulin Response, and Testing of its Reproducibility

The individual glucose and insulin values and the derived I/G of the first group of 14 men are shown in table 1.

When all I/G and G values at 10, 20, and 30 minutes were set against each other a positive correlation was found ($n = 42$, $r = 0.54$, $p < 0.001$).

This means that the higher the glucose level the higher the I/G will be. In order to show the positive relation between I/G and G for each individual we connected the I/G values of the lowest and highest G value during the 10-to-30-minute interval (figure 2). All 14 lines have a positive slope (sign test $p < 0.01$). The formula for the line with the mean slope through the means of I/G and G is

$$I/G = 0.0118\ (G - 68.56).$$

Since this formula probably approaches the part of the insulin-glucose dose-response curve for glucose values on the ascending limb of the glucose curve after loading, we chose the slope of this line as a parameter of the beta-cell response to oral glucose. We called the slope corrected insulin response (CIR) and defined it for convenience of calculation as:

$$CIR = \frac{I \cdot 100}{G(G-70)}$$

(I in μU./ml. and G in mg./100 ml., rising and above 80). CIR can be calculated for any point on the ascending limb of the glucose curve and should be independent of the glucose level in each individual. No relation to the glucose level can be demonstrated when the CIR of the lowest and the highest glucose level in the 10-to-30-minute interval are connected (sign test of the individual slopes; see figure 3). However, when all these points are used and their individual bonds neglected, a significant negative correlation is found ($r = 0.37$, $p = 0.05$). After a fixed oral glucose load the highest glucose levels are reached in subjects

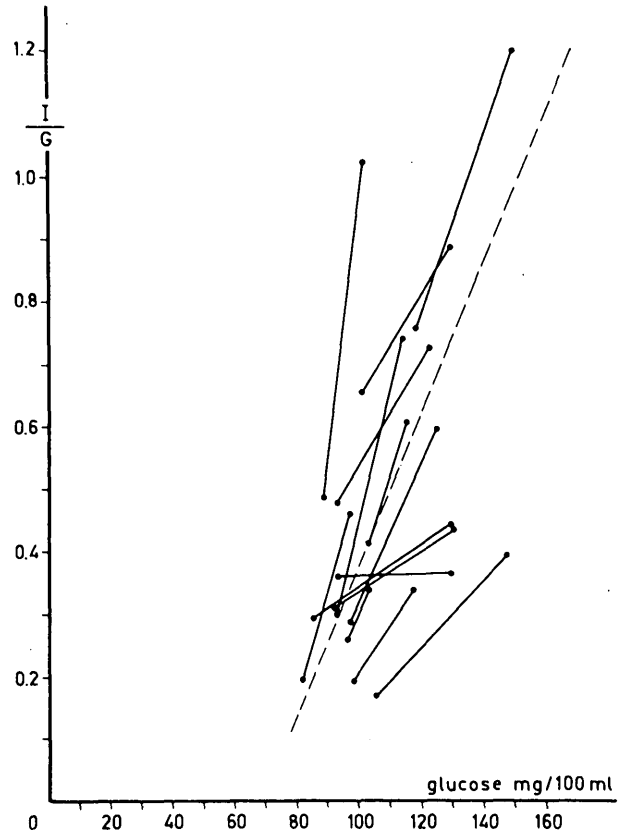

FIG. 2. Relation between I/G and G in 14 normal individuals. The points for the minimal and maximal G level reached between 10 and 30 minutes after oral glucose loadings are connected. The interrupted line is the line with the mean slope through the means of I/G and G.

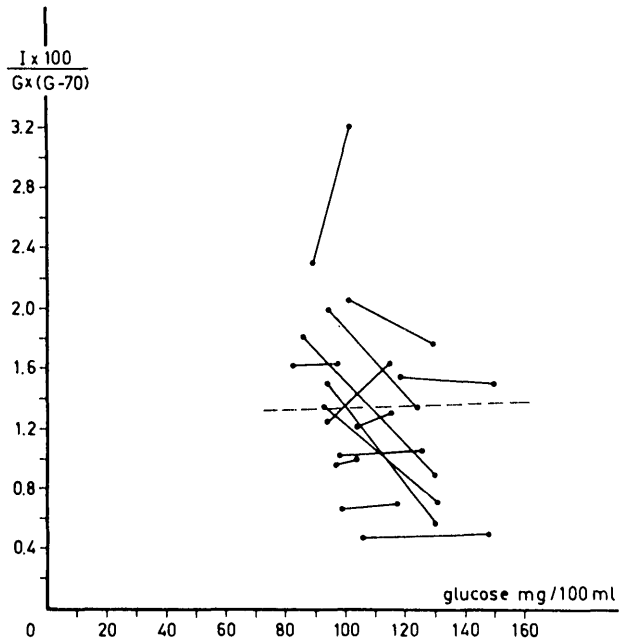

FIG. 3. Relation between CIR and G in 14 normal subjects. The points for the minimal and maximal G level reached between 10 and 30 minutes after oral glucose loadings are connected. The interrupted line is the line with the mean slope through the means of CIR and G.

with the lowest CIR. This emphasizes the meaning of CIR as a parameter of beta-cell function.

The data of consecutive GTTs in 10 individuals to test the reproducibility of CIR are given in table 2. The S.E.M. for CIR at 10, 20, and 30 minutes varied 1.6-13.7 per cent per individual, with a mean of 8.5 per cent. The variations of CIR during one test were smaller than this.

DISCUSSION

By approximating the relation of insulin to glucose levels after oral glucose loading we tried to find a parameter that measures the insulin response *independently* of the basal or reached glucose level. We deduced a glucose-independent parameter:

$$CIR = I \cdot 100/G(G-70)$$

The limitations of the insulinogenic index $\Delta I/\Delta G$ can be derived as follows: By use of our definition

$$I/G = (CIR/100)(G-70) \quad (1)$$

it was shown that CIR is rather constant in the same individual.

TABLE 2

Reproducibility of CIR 10-30. Consecutive GTTs in 10 subjects, with an interval of at least two days. G = glucose in mg./100 ml., I = immunoreactive insulin in μU./ml., CIR = corrected insulin response (see text). $\overline{CIR}$ is the mean of CIR at 10, 20, and 30 minutes, provided G is rising and above 80 mg./100 ml.

Subject	GTT	G			I			CIR			$\overline{CIR}$	S.E.M. in %
		10	20	30	10	20	30	10	20	30		
N d V	1	77	92	122	13	60	180		3.05	2.84	2.94	
	2	80	113	135	54	160	220		3.29	2.51	2.90	6.7
	3	87	108	106	55	160	220	3.72	3.90		3.81	
JBvdG	1	94	96	105	34	66	55	1.47	2.35	1.50	1.77	13.7
	2	94	136	154	35	95	120	1.51	1.06	0.94	1.17	
H P	1	106	126	127	45	85	80	1.18	1.90	1.11	1.16	8.5
	2	99	126	128	20	70	60	0.70	0.98	0.80	0.83	
MvL-T	1	115	142	153	26	49	54	0.50	0.48	0.43	0.47	
	2	117	135	136	27	28	40	0.49	0.31	0.45	0.42	6.7
	3	110	132	143	12	28	38	0.27	0.34	0.36	0.33	
PHvdK	1	105	107	96	65	65	45	1.77	1.64		1.71	1.6
	2	100	114	110	50	85	70	1.70	1.67		1.69	
FHvdK	1	119	137	130	35	85	95	0.60	0.93		0.76	
	2	114	132	151	45	90	85	0.90	1.11	0.70	0.90	10.3
	3	117	165	191	35	70	145	0.64	0.45	0.63	0.57	
JvdL-K	1	120	138	143	50	65	75	0.83	0.69	0.72	0.75	
	2	104	116	113	30	50	48	0.85	0.94		0.89	12.2
	3	107	108	94	45	65	30	1.14	1.55		1.36	
KvdG	1	99	112	110	20	32	38	0.70	0.67		0.68	
	2	114	147	160	45	75	75	0.88	0.66	0.53	0.69	8.1
	3	102	148	142	18	55	65	0.55	0.47		0.51	
J K	1	141	154	165	68	70	65	0.68	0.54	0.42	0.55	
	2	140	148	160	60	85	95	0.61	0.74	0.66	0.67	7.3
	3	119	146	166	35	60	55	0.60	0.54	0.35	0.50	
SJMvdG-B	1	116	148	171	48	170	240	0.90	1.46	1.39	1.25	
	2	128	175	176	85	160	240	1.13	0.87	1.30	1.10	10.5
	3	123	164	172	40	95	145	0.61	0.62	0.83	0.69	

Therefore $I_0 = (CIR/100) \cdot G_0 (G_0—70)$ and

$$I_t = (CIR/100)\, G_t (G_t—70)$$

ΔI is represented by $I_t—I_0$

$$\Delta I = \Delta G(CIR/100)(G_t + G_0—70) \quad (2)$$

and $\Delta I/\Delta G$ is represented by

$$\Delta I/\Delta G = CIR/100\,(G_t + G_0—70) \quad (3)$$

When 1 is substituted in 3,

$$\Delta I/\Delta G = I_t/G_t + CIR/100 \cdot G_0$$

In one individual the variation of I/G with the glucose level will be small compared to the fixed value of $G_0 \cdot CIR/100$. Therefore $\Delta I/\Delta G$ will mainly depend on the product of CIR and G_0, which two parameters are mutually dependent and probably inversely related. As a consequence, $\Delta I/\Delta G$ will not change greatly until the glucose peak is reached. After the top of the glucose curve has been reached the glucose values will decrease with a speed correlated to glucose tolerance (comparable to the K value[4]), while the insulin values will decline according to its biologic half-life after a short further rise. Accordingly, $\Delta I/\Delta G$ will promptly increase after the top of the glucose curve has been reached. This increase is not an expression of better beta-cell function but rather a marker of glucose tolerance. It can be seen from figure 3 in Seltzer's article[1] that $\Delta I/\Delta G$ does increase after the glucose peak. From our own material we drew two individual curves to show this phenomenon (figure 4). As a consequence, the comparison of two groups at empirically chosen fixed intervals by means of the insulinogenic index becomes impossible when the individuals studied reach the glucose peak at different times.

One should hesitate to apply CIR to the fasting state, as the relationship between glucose and insulin is influenced by several regulatory systems in that situation and fasting insulin measurements are subject to a relatively large error.

In summary, we deduced from the physiologic relation between glucose and insulin a reproducible parameter of the insulin response from 10 to 30 minutes after an oral glucose load rather than determining an empirical ratio. By using this parameter CIR $= I \cdot 100/G(G-70)$ one will be able to evaluate the pancreatic function during an oral GTT independently of the glucose level. This makes it possible to compare the same individual under different conditions or different individuals under identical circumstances.

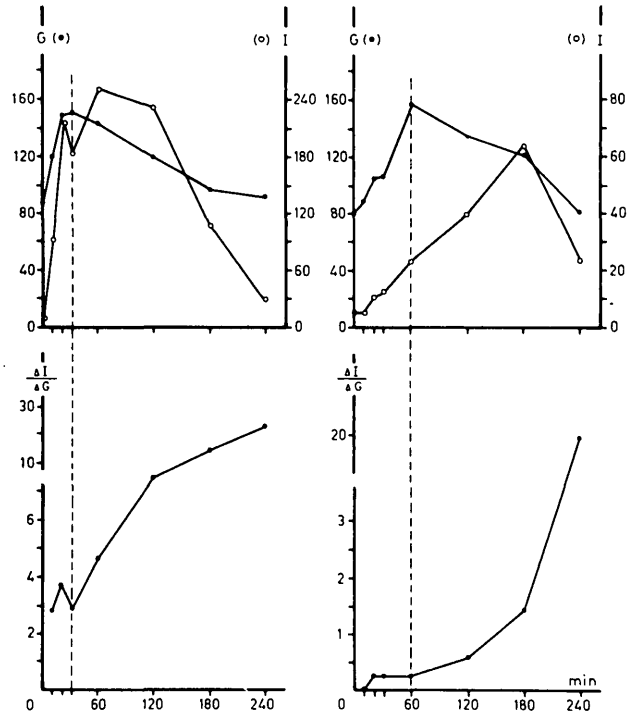

FIG. 4. The insulinogenic index $\Delta I/\Delta G$ in relation to glucose and insulin levels after oral glucose loading in two normal subjects. The insulinogenic index apparently rises after the glucose peak (indicated by the vertical interrupted line) has been reached.

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