Glucose Tolerance and Insulin Release, A Mathematical Approach

II. Approximation of the Peripheral Insulin Resistance After Oral Glucose Loading

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SUMMARY

A parameter of peripheral insulin activity ($A = 10^4/I_pG_p$) can be obtained after oral glucose loading by simple calculation using insulin and glucose levels at the glucose peak. In combination with a glucose-independent parameter of beta-cell function (CIR = 100 · I/G(G-70)) a parameter of glucose tolerance (GT = A · CIR) is defined. The parameters allow one to separate the contributions of beta-cell function and peripheral insulin resistance to the glucose tolerance observed after glucose loading. Examples, based on the literature and our own work, illustrate the increase of A and GT after weight reduction and the decrease of A and GT by cortisone acetate premedication as well as long-term oral contraceptive medication. DIABETES *25*:245-49, April, 1976.

The oral glucose tolerance test (GTT) is used to obtain information about the resultant of the beta-cell secretory function and the peripheral action of insulin. The measurement of insulin levels after an oral glucose load does not separate these two mechanisms completely, and more elaborate procedures such as the intravenous glucose tolerance test and the determination of peripheral resistance[1] are needed.

The aim of this report is to try to separate, with the simple use of glucose and insulin levels measured after oral glucose loading, the pancreatic and peripheral contribution to the observed "glucose tolerance."

As mentioned in part I,[2] CIR may be a useful parameter of beta-cell function. In part II we will concentrate on peripheral insulin resistance.

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CALCULATION OF PERIPHERAL INSULIN ACTIVITY AND GLUCOSE TOLERANCE

Once glucose has entered the blood stream, it is removed from this compartment mainly by the mediation of insulin. Apart from factors influencing glucose absorption, the glucose levels reached after an exogenous load are governed by the beta-cell function as well as by the activity of insulin at the site of action. Peripheral insulin resistance has been deduced from the glucose level reached during constant infusion of glucose, insulin, propranolol, and epinephrine.[1,3] When the steady state has been reached during this test, glucose removal will match the infusion speed and will be a function of the glucose level (G), the insulin level (I), and the peripheral insulin activity factor (A). As the glucose infusion speed is constant and the insulin levels reached are the same in all individuals, A will be inversely related to G. However, as the glucose absorption rate in an individual is constant during a long interval after oral glucose loading independent of the size of the load,[4] and individual variations of absorption rate are small and not different between normals and diabetics,[5] we wondered if we were able to approximate A from oral glucose tolerance tests. Provided the glucose peak is reached during the period of constant glucose absorption, the same relations as cited for the infusion studies exist at the moment the glucose peak is reached.

To approximate the insulin activity A in individuals with data from the oral GTT, we need, besides the glucose level, the insulin level, as it is not kept constant, as it is in the infusion method cited above.

Let us define $A = 10^4/I_pG_p$ (1)

using the insulin and glucose values at the glucose peak in μU./ml. and mg./100 ml., respectively. One

must be aware of the fact that A will be spuriously influenced by intestinal absorption abnormalities and glucose loss in the urine and that the real glucose peak may be missed during a test.

Combination of the peripheral insulin activity A and a glucose-independent parameter of beta-cell function should yield a parameter of glucose tolerance. As we reported $CIR = 100 \cdot I / G(G-70)$ (2) to be such a parameter of beta-cell function, we will define the product of A and CIR as a glucose-tolerance parameter (GT). In formula:

$$GT = A \cdot CIR \quad (3)$$

Substitution of the formulas (1) and (2) in (3) results for the glucose peak in:

$$GT_p = 10^6/Gp^2 \cdot (Gp-70) \quad (4)$$

This shows that indeed GT may be a fair parameter of glucose tolerance, since the only variable is the glucose level reached.

The classic criteria of glucose tolerance mostly use one or more glucose levels after the oral glucose load, e.g. at 60, 90, or 120 minutes. Formula 4 does not regard an empirically fixed time interval but applies to the glucose peak irrespective of the moment it is reached. This moment may be different in individuals, so probably GT has a more significant meaning than the glucose levels at arbitrarily chosen intervals of 60, 90, or 120 minutes. In case CIR at the glucose peak (CIR_p) is lower than CIR during the initial phase of the GTT, intratest decrease of glucose tolerance (GT versus GT_p) can be observed. Thus, criteria based on GT and GT_p are equivalent to criteria based on glucose levels at the glucose peak and 120 minutes. To give an idea of the magnitude of GT, a glucose peak reached during a GTT of 160 mg./100 ml. can be translated into a GT value of 0.43.

To show the usefulness of the defined parameters, we applied them to work reported by others as well as to our own material.

APPLICATION OF THE PARAMETERS TO MATERIAL PROVIDED BY THE LITERATURE

First, to test the whole idea, the described principles were applied to the material reported by Olefsky et al.[3] As not all individual values are given, we used the means given in the tables and figures. An oral glucose tolerance test was performed by them in 36 obese persons, before and after weight reduction. In 10 of them an infusion study with glucose, insulin, propranolol, and epinephrine was performed to establish insulin resistance. The mean values derived from this article and the parameters calculated from them are shown in tables 1 and 2.

TABLE 1

Data from Olefsky et al.[3] concerning mean values during an oral glucose tolerance test in 36 obese subjects before and after weight reduction, followed by the parameters for beta-cell function, insulin activity, and glucose tolerance derived by us. (Indices refer to the time after the start of the test, p refers to values at the glucose peak).

	G_{30}	G_p	I_{30}	I_p	CIR	CIR_p	A	GT	GT_p
Before	165	182	125	158	0.80	0.77	0.35	0.28	0.27
After	151	161	84	95	0.69	0.65	0.65	0.45	0.42

Tested with oral glucose, glucose tolerance (GT) improves after weight reduction. This is primarily due to improvement of peripheral insulin activity (A). The same phenomenon is observed in the infusion study: glucose remains at a lower level after weight reduction, so A_i calculated from G and I during infusion improves.

After weight reduction the value of A_i in the infusion study is the same as that of A in the oral test. This would mean that the influx of glucose in the circulation from intestinal absorption after passage through the liver matches the intravenous infusion speed of 6 mg./kg./min., or about 500 mg./min. Indeed, Rehfeld and Stadil[5] have been able to mimic the oral glucose curve by constant infusion of about 550 mg./min. for the period in which the glucose peak in the oral curve was reached. This approximates the value that can be deduced from the report of Della Corte et al.[6]

However, the values of A (oral) and A_i (infusion) differ before weight reduction. This can be explained by urinary glucose loss, since the mean glucose level during the infusion study is 241 mg./100 ml., causing a spuriously elevated A_i. If the real value of A_i is 0.35, as in the oral test, ⅛ of the infused load would be lost in the urine. The average weight was 85 kg., so the average infusion speed was 510 mg./min. Therefore the average loss in the urine would be $⅛ \cdot 510 = 64$ mg./min. Taking a glomerular filtration rate of 100 ml./min., we arrive at a threshold for

TABLE 2

Mean plateau levels during constant infusion of glucose, insulin, propranolol, and epinephrine. Data from Olefsky et al.[3] in 10 obese subjects before and after weight reduction, followed by the parameter for insulin activity calculated by us.

	G	I	A_i
Before	241	104	0.40
After	161	94	0.66

TABLE 3

(A) Data from Bagdade et al.[7] of oral glucose tolerance tests in eight obese subjects before and after weight reduction, followed by the derived parameters (from subjects 6 and 7 no data on oral tests were included in the publication).
(B) Mean values in six obese controls from Bagdade et al.[7] and the calculated parameters. Legends as in table 1; CIR is averaged from 15- and 30-minute values, provided G was rising and above 80 mg./100 ml.

	Subject	G_{15}	G_{30}	G_p	I_{15}	I_{30}	I_p	CIR	CIR_p	A	GT	GT_p
(A)	1 Before	99	128	151	69	218	298	2.67	2.44	0.22	0.59	0.54
	After	105	140	156	131	174	174	2.67	1.30	0.37	0.99	0.48
	2 Before	78	129	137	202	500	320	6.57	3.49	0.23	1.51	0.80
	After	98	114	123	131	107	84	3.45	1.29	0.97	3.34	1.25
	3 Before	93	100	162	152	169	470	6.37	3.15	0.13	0.83	0.41
	After	99	95	128	94	62	128	2.94	1.72	0.61	1.79	1.05
	4 Before	95	138	157	368	668	668	11.30	4.89	0.10	1.13	0.49
	After	93	112	132	224	376	720	9.23	8.80	0.11	0.97	0.93
	5 Before	118	144	196	115	195	382	1.93	1.55	0.13	0.26	0.21
	After	97	106	156	60	39	62	1.66	0.41	1.03	1.72	0.42
	8 Before	140	178	226	63	73	134	0.51	0.38	0.33	0.17	0.13
	After	111	151	181	38	60	90	0.66	0.45	0.61	0.41	0.28
	9 Before	151	190	240	83	133	158	0.63	0.39	0.26	0.17	0.10
	After	163	213	275	88	92	146	0.59	0.26	0.25	0.15	0.06
	10 Before	150	208	284	76	102	250	0.50	0.41	0.14	0.07	0.06
	After	101	126	176	214	180	234	4.69	1.25	0.24	1.14	0.30
	Mean											
	Before							3.81	2.09	0.19	0.59	0.34
	After							3.24	1.94	0.52	1.31	0.60
(B)	6 Controls	86	116	131	100	193	255	5.45	3.19	0.30	1.63	0.95

glucose of 241 − 64 = 177 mg./100 ml.!

As a consequence, A calculated from oral tests probably is a good approximation of the same parameter (A_i) measured in the infusion studies. Besides that, the other parameters CIR and GT also match the authors' conclusions.

We must keep in mind that all calculations were performed on mean values, and no conclusions can be drawn in the individual cases. Bagdade et al.[7] reported individual data of oral glucose tests in eight extremely obese persons before and after weight reduction. The reported values used for calculation and the resulting parameters are given in table 3A.

Again "early" glucose tolerance (GT) during the first half hour, as well as "late" glucose tolerance (GT_p) improve ($p < 0.05$) by improvement of A ($p < 0.05$) after weight reduction, while CIR and CIR_p do not change (Wilcoxon, paired test). Intratest decreasing of beta-cell reserve is demonstrated in all persons, before as well as after weight reduction. (N.B. One should note that after weight reduction overweight persisted; only one person [no. 2] reached normal weight.) In the same article the mean values of six obese controls with a completely normal glucose tolerance are reported. The calculated parameters for these means are given in table 3B. It is obvious that their normal glucose tolerance is primarily due to their higher, but still subnormal, peripheral insulin activity A, combined with clear hyperinsulinism. In this control group intratest decreasing CIR is again observed.

Therefore, the application of our parameters to data of individual patients from the article by Bagdade et al. and to the mean values of the report by Olefsky et al. proves equally useful.

The phenomenon of intratest declining CIR in obesity drew our attention to the observed differences in glucose tolerance during the day. In a recent report on these differences, Zimmet et al.[8] compared morning and afternoon oral glucose tests. The reported mean values of their total group of 31 persons and the derived parameters are shown in table 4. From these data it may be concluded that glucose tolerance in the afternoon is not decreased by an increase of peripheral insulin resistance but by an intratest decrease of CIR. This phenomenon can be observed in all their subgroups according to age, sex, or weight, and therefore seems to be unrelated to these factors. Whether the intratest decrease of the CIR indicates exhaustion of

TABLE 4

Means of glucose tolerance tests from Zimmet et al.[8] in 31 persons. Oral tests performed during the morning compared to afternoon oral tests. Parameters for beta-cell function, insulin activity, and glucose tolerance were derived from the means. Legends as in table 3.

	G_{30}	G_p	I_{30}	I_p	CIR	CIR_p	A	GT	GT_p
Morning	119.1	125.9	35.5	43.6	0.61	0.75	1.82	1.11	1.37
Afternoon	110.8	146.6	27.8	37.7	0.61	0.34	1.81	1.06	0.60

TABLE 5

GTT and cortisone GTT parameters for beta-cell function, insulin activity, and glucose tolerance in 10 females, before use of Lyndiol and during Lyndiol medication. Legends as in table 3

Before						During Lyndiol use					
	GTT			Cortisone GTT			GTT			Cortisone GTT	
CIR	A	GT	CIR	A	GT	CIR	A	GT	CIR	A	GT
0.98	0.81	0.79	0.68	0.75	0.51	0.57	0.75	0.43	0.19	0.47	0.09
1.75	1.04	1.82	1.74	0.09	0.16	1.78	0.54	0.96	1.49	0.10	0.15
1.12	0.94	1.05	2.39	0.17	0.41	3.97	0.26	1.03	1.84	0.29	0.53
2.35	1.69	3.97	2.35	0.57	1.34	1.54	0.63	0.97	1.26	0.35	0.44
0.92	0.49	0.45	1.40	0.24	0.34	1.28	0.55	0.70	0.94	0.29	0.27
0.75	1.65	1.24	0.52	1.01	0.53	0.49	0.84	0.41	0.47	0.24	0.11
2.18	0.63	1.38	1.38	0.63	0.87	1.37	0.73	1.00	1.10	0.34	0.37
0.64	2.02	1.29	0.75	0.98	0.74	0.48	1.27	0.61	0.49	0.34	0.17
0.56	1.30	0.73	0.96	0.56	0.54	0.82	0.86	0.71	0.61	0.33	0.20
1.35	1.28	1.73	0.88	0.48	0.42	0.54	0.52	0.28	0.66	0.55	0.36

the beta cells or reflects some kind of inhibition of insulin release remains unsolved; but the decreased insulin response in the afternoon compared to morning tests observed in the same department[9] after an intravenous glucose load may be the expression of a similar mechanism.

APPLICATION OF THE PARAMETERS TO OUR OWN MATERIAL

Methods. In 10 nondiabetic females of normal weight, studies were performed before the use of the oral contraceptive Lyndiol 2.5 (2.5 mg. lynestrenol and 0.075 mg. mestranol) and after a medication interval of six to 19 cycles (mean 13.7 cycles). In 10 females without a family history of diabetes, the same studies were performed during Lyndiol administration and in the first month after stopping this medication. Mean duration of medication was 27 cycles (range three to 58 cycles).

Between the 18th and 23rd day following the first day of the last menstruation or withdrawal bleeding, two oral glucose tolerance tests were performed with a 100-gm. load. The second test was performed within two or three days after the first one, after a premedication of 50 mg. cortisone acetate at 12 and two hours before the start of the test. At least 300 gm. of carbohydrates had been used daily for at least three days before the test. Blood samples were taken at 0, 15, 30, 60, 90, 120, and 150 minutes.

Glucose was measured by a ferricyanide method on an AutoAnalyzer in whole venous blood. Plasma insulin was measured by radioimmunoassay; samples of one person were assayed in one run.

This material forms a part of the work published earlier by one of us (P.T.[10]).

TABLE 6

Glucose tolerance tests before and during use of Lyndiol. Mean values of the parameters in table 5 and the significance of the differences (Wilcoxon, paired observations).

		GTT				Cortisone GTT		
		CIR	A	GT	p	CIR	A	GT
Before	CIR	1.26			n.s.	1.31		
	A		1.19		<0.01		0.55	
	GT			1.45	<0.01			0.59
	p	n.s.	<0.02	<0.01		<0.01	n.s.	<0.02
During	CIR	1.28			<0.02	0.91		
	A		0.70		<0.01		0.33	
	GT			0.71	<0.01			0.27

RESULTS

The results of the restudy of our own material are compiled in tables 5 to 8. It can be concluded that Lyndiol medication decreases glucose tolerance by enhancement of peripheral resistance without affecting beta-cell function. Before and during use of Lyndiol, cortisone premedication enhances peripheral resistance, causing a decreased glucose tolerance. However, cortisone premedication during the use of Lyndiol results in a decreased CIR (exhaustion?) in contrast to the situation before contraceptive medication. The decrease of the CIR in the cortisone GTT during Lyndiol administration combined with the drastically decreased peripheral insulin activity results in a sharp decline of glucose tolerance; indeed several cortisone GTTs were clearly abnormal.

After Lyndiol withdrawal no differences can be detected in a GTT within a month. However, after cortisone premedication differences come to light, CIR does not change any more after cortisone premedication and peripheral insulin activity decreases less after cortisone than during Lyndiol use, resulting in a bet-

TABLE 7

GTT and cortisone GTT parameters for beta-cell function, insulin activity, and glucose tolerance in 10 females, during Lyndiol medication and in the first month after withdrawal of Lyndiol. Legends as in table 3

During Lyndiol						After withdrawal					
GTT			Cortisone GTT			GTT			Cortisone GTT		
CIR	A	GT	CIR	A	GT	CIR	A	GT	CIR	A	GT
1.52	1.56	2.37	0.86	0.41	0.35	2.95	0.77	2.27	1.55	0.38	0.59
2.63	0.40	1.05	1.32	0.15	0.20	3.14	0.42	1.32	2.94	0.28	0.82
1.28	0.55	0.70	0.94	0.29	0.27	1.02	0.42	0.43	0.98	0.47	0.46
0.48	1.27	0.61	0.49	0.34	0.17	0.46	2.06	0.95	0.28	0.91	0.25
0.82	0.86	0.71	0.61	0.42	0.26	0.73	0.51	0.37	0.85	0.50	0.43
0.58	0.51	0.30	0.58	0.48	0.28	1.27	0.66	0.84	0.87	0.32	0.28
0.92	1.14	1.05	0.21	0.54	0.11	0.37	1.03	0.38	0.53	0.76	0.40
1.12	0.38	0.43	1.14	0.17	0.19	1.19	0.48	0.57	0.85	0.16	0.14
0.49	1.10	0.54	0.31	0.81	0.25	0.29	1.89	0.55	0.43	1.22	0.52
0.64	0.68	0.44	0.64	0.38	0.24	1.25	0.72	0.90	0.75	0.90	0.68

TABLE 8

Glucose tolerance tests during and after stopping Lyndiol medication. Mean values of the parameters in table 7 and the significances of the differences (Wilcoxon, paired test)

		GTT				Cortisone GTT		
		CIR	A	GT	p	CIR	A	GT
	CIR	1.05			<0.05	0.71		
During	A		0.85		<0.01		0.40	
	GT			0.82	<0.01			0.23
	p	n.s.	n.s.	n.s.		n.s.	<0.05	<0.01
	CIR	1.27			n.s.	1.00		
After	A		0.89		<0.05		0.59	
Withdrawal	GT			0.86	<0.05			0.46

ter tolerance. Probably the interval after the withdrawal of contraceptive medication was too short to detect reversibility in the GTT. Whether the differences in the cortisone GTT are really reflections of reversibility of the process or have to be explained by the longer half life of cortisone during oral contraceptive medication is hard to say, as discussed in the original publication.[10]

CONCLUSION

By the use of rather simple calculations, a parameter for peripheral insulin activity (A) was derived from insulin and glucose levels obtained after oral glucose loading. As judged from reported data in the literature and from our own material, this parameter fairly approximates the peripheral insulin activity. Combined with a parameter of beta-cell-secretory function (CIR) a glucose tolerance parameter (GT) can be obtained. Changes in these parameters by well-known principles, such as weight reduction, are in accordance with generally accepted theories on glucose metabolism.

We feel that with the use of these parameters a proper separation can be made between the contribution to oral glucose tolerance of beta-cell function and peripheral insulin resistance, especially when testing the same individual under different circumstances or different individuals under the same circumstances.

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