



**EFFECT OF SHORT-TERM TOLBUTAMIDE TREATMENT ON INSULIN  
DYNAMICS IN NEWLY DIAGNOSED OBESE AND NON-OBESE  
ADULT DIABETICS**

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**PUBLICAÇÃO IEA N.º 197**  
Fevereiro — 1970

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CIDADE UNIVERSITÁRIA "ARMANDO DE SALLES OLIVEIRA"  
SÃO PAULO — BRASIL

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\* Reprinted from Hormone and Metabolic Research, vol. 2, nº 1, pg. 6-8, 1969.

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SUMMARY

Blood glucose and plasma insulin response to oral glucose and I.V. tolbutamide were measured before and after 2-month oral treatment with tolbutamide in 5 patients with maturity-onset diabetes. The improvement in glucose tolerance was not associated with an increase in plasma insulin, but with a decrease in its output, after I.V. tolbutamide, in the non-obese and no change in the obese, probably related to the maintenance of obesity and the insulin antagonism associated with it.

Despite the knowledge that short-term sulfonylurea treatment is followed by an improvement of glucose tolerance with no change or a decrease in insulin levels (Sheldon, Taylor and Anderson, 1966; Reaven and Dray, 1967), there are no studies on sulfonylurea-stimulated prestored insulin secretion, after stopping the drug treatment. In this paper we present the initial results of two groups of diabetics, obese and non-obese, treated with tolbutamide, without dietary restriction.

MATERIAL AND METHODS

Five newly diagnosed diabetic outpatients, none previously treated, were studied. Their ages ranged from 36 to 55 years. Two patients (MEC and MLM) were obese (body weight more than 15% above ideal body weight, obtained from the tables of Desirable weights for men and women, Metropolitan Life Insurance Company, Statistical Bureau (McBryde, 1964)). Two of the non-obese diabetics were considered to be "mild diabetics", since their fasting blood

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sugar was below 105 mg per 100 ml (HG and NG). The remaining non-obese (TC) and the two obese subjects were designated as "severe diabetics". Their fasting blood sugars were above 200 mg per 100 ml.

Each patient underwent two studies, before and after tolbutamide treatment: 1) oral glucose tolerance test (1.75 gm. of glucose per kilogramme of ideal body weight and venous blood drawn before, 1/2, 1, 1 1/2, 2 and 3 hours after glucose ingestion) and 2) intravenous tolbutamide tolerance test (1 gm. of tolbutamide injected intravenously and venous blood drawn before and 5, 10, 20, 30, 40, 60, 90 and 120 minutes after the injection).

In all samples blood sugar was measured by the Nelson modification of the Somogyi method (Nelson, 1944), and plasma insulin by the method of Yalow and Berson (1960). Each patient received tolbutamide in a dosage of 1 gm. daily, given in the morning, for two months. The oral glucose tolerance test was repeated 3 weeks and the tolbutamide test 4 weeks after stopping the sulfonylurea treatment. During the study the patients were instructed to maintain the same diet as before starting the tolbutamide treatment without any restriction in carbohydrate intake. Individual weight changes were minimal during the study and increased slightly in two of the patients (TC and MEC).

Since methods are not available which permit direct measurement of pancreatic insulin secretion in man, the areas circumscribed by the plasma insulin response curves were used as an index for comparing relative quantitative changes of insulin secretion. The units used to express this function of insulin secretion are  $\mu\text{U/ml/min}$ .

## RESULTS

The results are indicated in Table 1.

Table 1. Blood Glucose and Plasma Insulin Responses to oral Glucose and I.V. Tolbutamide before (B) and after (A) Tolbutamide Therapy.

Name (age, sex)	Height (cm)	Weight (Kg)	Glucose Tolerance Test (GTT) Blood Glucose (mg/100 ml) Time (min.)						Plasma Insulin ( $\mu$ U/ml) Time (min.)					
			0	30	60	90	120	180	0	30	60	90	120	180
T.C. (55 y, female)	157	B 60	300	400	509	600	600	600	19	44	62	75	95	42
		A 61.5	100	164	229	336	209	183	15	60	120	51	21	12
H.B. (36 y, female)	162	B 55.3	73	162	239	239	208	176	7	14	32	47	22	8
		A 55.8	62	115	187	187	182	125	14	18	40	51	19	7
N.G. (47 y, male)	156	B 58.7	90	219	268	226	162	63	2	4	43	57	42	11
		A 58.0	78	141	205	198	113	62	9	15	35	48	26	17
M.E.C. obese (36 y, female)	155	B 85.0	228	263	342	330	318	280	18	28	76	117	39	23
		A 87.0	140	175	239	231	170	170	14	43	60	50	32	11
M.L.M. obese (49 y, female)	150	B 63.0	222	296	377	393	411	329						
		A 63.0	200	250	299	277	250	200	16	40	74	191	82	47

Name (age, sex)	I.V. Tolbutamide Tolerance Blood Glucose (mg/100 ml) Time (min.)										Test						Plasma Insulin ( $\mu$ U/ml) Time (min.)						Plasma Insulin Area ( $\mu$ U/ml. min. obese $10^{-2}$ )
	0	5	10	20	30	40	60	90	120	0	5	10	20	30	40	60	90	120	GTT	I.V. Tolbutamide			
T.C. (55 y, female)	253	250	250	250	220	200	200	261	20	28	35	48	60	85	136	59	48	49	45.5				
	147	118	118	108	97	97	78	75	85	15	17	20	50	35	34	6.5	7	5	48	9.5			
H.B. (36 y, female)	66	64	64	61	61	43	40	55	60	17	28.5	40	68	96	118	85	57	20	22.5	58.5			
	62	62	62	52	48	39	37	43	43	10	11	20	41	36	20	17	14	6	22.5	11.8			
N.G. (47 y, male)	88	88	78	44	27	27	27	57	67	7.5	14	18	50	76	99.5	62	27	15	33.5	42.5			
	77	77	50	40	36	23	53	69	60	13	42	90.5	61	36	36	26.5	24	16	21.7	22.5			
M.E.C. obese (36 y, female)	161	161	161	148	137	137	123	110	110	20	22	32	63	110	102	32	25	18	45	33			
	141	141	137	123	99	94	94	86	86	15	32	63	78	69	47	39	28	18	33	30			
M.L.M. obese (49 y, female)	211	211	200	189	189	189	151	130	120	25	40	60	91	110	118	138	98	39	74				
	197	190	180	170	137	100	80	80	82	35	40	48	60	105	140	191	100	65	71	72			

All patients were considered as being good responders to tolbutamide, on the basis of the reduction of 16 per cent or more in the area subscribed by the 2nd. glucose tolerance curve in relation to the control test, according to Sheldon, Taylor and Anderson (1966), despite the 3 week period without the sulfonylurea.

The total insulin output, estimated by the area circumscribed by the plasma insulin curve, decreased in two patients (NG and MEC) while in the remaining two (TC and HB) there was no change. The blood glucose responses to 1 gm. of tolbutamide intravenously were variable in the control test: patient TC, with severe diabetes, demonstrated a greatly impaired glucose response when compared to the obese diabetics, also considered as having a severe form of the disease. After tolbutamide therapy, the responsiveness to

the I.V. injection of the drug, increased in all patients with severe diabetes whereas there were no changes in glucose response in relation to the control test in the mild diabetics (HB and NG).

Tolbutamide-stimulated insulin secretion evaluated by the area under the insulin curve, in the non-obese diabetics, showed a great decrease. On the other hand, the insulin secretion, in the obese patients, did not change significantly after treatment. However, the peak of insulin release, in all patients except MLM, occurred at an earlier time after sulfonylurea treatment, when compared to the initial test.

#### COMMENTS

As previously observed with diabetics treated with chlorpropamide (Reaven and Dray, 1967) and acetohexamide (Sheldon, Taylor and Anderson, 1966), improvement in glucose tolerance was not associated with an increase in serum or plasma insulin concentration, after long-term treatment with the sulfonylurea. Instead, there was a decrease or no change in insulin levels.

There is now considerable evidence indicating that tolbutamide and glucose stimulate pancreatic secretion of insulin and does not stimulate the mechanism of insulin biosynthesis, whereas glucose acts not only on the pool of pre-stored insulin but also on another insulin pool closely associated with its synthesis (Curry, Bennett and Grodsky, 1968).

It is, therefore, not surprising that the plasma insulin responses to tolbutamide differed somewhat from those observed with glucose. Thus, the non-obese diabetic, independently of the severity of the disease (as indicated by the glucose tolerance test) showed a great decrease in tolbutamide stimulated pre-stored insulin secretion, after stopping the drug treatment, with the persistence of the improvement of beta-cell function.

On the other hand, the obese diabetics, despite the persistent improvement of glucose tolerance, did not show a decrease in the insulin release after i.v. tolbutamide. This effects is probably related to the maintenance of obesity and the insulin antagonism associated with it (Perley and Kipnis, 1966).

In conclusion, diabetic patients, undergoing therapy with sulfonylurea, demonstrate improvement in glucose tolerance and this cannot be attributed to an increase in the amount of circulating insulin. On the contrary, the improvement in glucose tolerance was accompanied by a decrease in pre-stored insulin, as indicated by the effect of an acute load of tolbutamide. When obesity was present, with its known antagonism to insulin, there was no change in the pool of releasable insulin, in the pancreas.

#### ACKNOWLEDGEMENT

This study was supported by a Grant from "Fundação de Amparo à Pesquisa do Estado de São Paulo" (66/429) and Hoechst to Brasil, São Paulo.

#### RESUMO

Respostas glicêmicas e da insulina plasmática a uma carga de glicose oral e à tolbutamida endovenosa, foram estudadas antes e após tratamento oral com tolbutamida em 5 pacientes, com diabetes do tipo adulto. A melhora na tolerância à glicose não estava associada com aumento na insulínia, havendo uma queda desta, após tolbutamida endovenosa nos não-obesos e sem alteração nos obesos, provavelmente relacionada a manutenção da obesidade e com o antagonismo à insulina nesta situação.

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