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Insulin, Glucagon and Growth Hormone in Primary Adult Myxoedema

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Summary. Previous studies have shown that in patients with primary adult myxoedema (PAM) the rise in blood glucose (BG) and plasma insulin (IRI) after various stimuli is higher and more sustained than in normals, so that in this condition insulin resistance may be hypothesized. In the search for factors involved glucose (BG), insulin (IRI), glucagon (IRG), (assayed with an antiserum which is not specific for pancreatic glucagon) and growth hormone (GH), have been determined in blood during the oral glucose tolerance test, OGTT, (100 g), arginine intravenous infusion, ATT (30 g/30 min), and insulin-induced hypoglycemia, ITT (0.1 kg), in patients with PAM, without clinical diabetes, and in normal control subjects. During OGTT, glucose and IRI levels were higher than normal; on the other hand, IRG (probably gut glucagon, or enteroglucagon) levels were lower than in normals. During ATT blood glucose in PAM was slightly higher than normal at 30′ and lower at 90′ and 120′; insulin levels were higher than normal at any time; GH and IRG (very likely pancreatic glucagon, or nesidioglucagon) responses were lower than normal. During ITT, blood glucose levels dropped slowly but progressively and GH levels were lower than normal. It is concluded that in primary adult myxoedema glucagon, both enteric and pancreatic, and growth hormone secretions are impaired. The resistance to insulin action observed in PAM does not seem to be due to an excess of growth hormone or (nesidioglucagon).

Key words: Primary adult myxoedema, oral glucose tolerance test, arginine test, insulin tolerance test, plasma insulin, pancreatic glucagon (nesidioglucagon), gut glucagon (enteroglucagon), growth hormone, hypoglycemia, insulin resistance.

In previous studies [1, 12, 2, 8, 16] an increased frequency of diabetes in primary adult myxoedema (PAM) has been observed, while the frequency of non iatrogenic myxoedema has been shown to be increased in large groups of diabetics [22, 12].

Insulin assays in the fasting state have demonstrated normal or supernormal levels in patients with primary adult myxoedema [10, 6, 14, 3, 4, 23, 25]; after various stimuli in these patients a rise to relatively high levels [16, 23, 20] and a slow return to basal values [3] have been observed; somewhat different findings were registered by others [26]. In our studies the behaviour of blood glucose and insulin levels indicated some degree of insulin resistance in primary myxoedema [3]. On the other hand, in patients with iatrogenic hypothyroidism insulin levels have been found lower than in normal subjects [7] and PAM patients [8]. Conflicting data have been obtained in experimental hypothyroidism [24, 17]. In order to clarify these findings and particularly to obtain a better understanding of carbohydrate metabolism in this condition we have undertaken a parallel study of insulin, glucagon and growth hormone levels in blood after provocative tests. To our knowledge few data have been reported by other authors on growth hormone [15, 5, 27] secretion and no data on glucagon levels in blood.

Methods

The study was conducted in a group of subjects with primary adult myxoedema (see Table 1) and a normal control group.

The diagnosis of primary adult myxoedema was established on the basis of clinical examination, PBI (less than 3 μg/100 ml) BMR (less than −20%), I^{131} thyroid uptake (absent or below 10%), antithyroglobulin antibodies (over 1:2500, in all cases according to Boyden's method) (s. Table 1). None of the individuals studied was grossly overweight.

Patients with clinical diabetes were excluded.

All subjects received a diet with 300 g of carbohydrate for at least three days before each test. The following tests were performed after an overnight fast.

1. Standard oral glucose tolerance test, OGTT (100 g per os); performed in 7 PAM subjects and in 8 normal subjects. Blood samples were taken in the fasting state and 30′, 60′ and 120′ after glucose administration.

2. Arginine test, ATT (30 g arginine hydrochloride diluted in 400 ml of water were infused at a constant rate for 30 min in the cubital vein): performed in 6 PAM subjects and in 7 normal subjects. Blood was taken from the contralateral cubital vein 30′ and 0′ before and 20′, 30′, 45′, 60′, 90′ and 120′ after the start of the infusion.

3. Insulin tolerance test, ITT (insulin, 0.1 units/kg b. w. was injected intravenously in 1 min): carried out in 6 PAM subjects and in 6 normal subjects. Blood was taken from the contralateral vein at 30′ and 0 min before, and 20′, 30′, 45′, 60′, 90′, 120′ after the injection.

Blood glucose was assayed by the Hoffman method [13] as applied to the Auto-Analyzer; plasma insulin (IRI) by the Hales and Randle radioimmuno-

assay [11], plasma glucagon[1] (IRG) by Lawrence's method [18], growth hormone (GH) by the method of Molinatti and others [21].

Results

Oral Glucose Tolerance Test (OGTT) Table 2

Blood glucose in the myxoedema group (PAM) is significantly higher than in normal subjects at 60′ and 120′.

Analysis of individual curves shows that 4 out of 7 subjects with PAM are clearly diabetic according to the criteria of Fajans and Conn [9].

Insulin Tolerance Test (ITT) Table 4

The administration of insulin to patients with PAM is followed by a fall in blood glucose which is considerably slower, but more persistent, than in normal subjects; significant differences are observed from 20′ to 120′; GH response in PAM is markedly reduced. Statistically significant differences are observed from 20′ to 90′.

Comment

The high frequency of abnormal glucose tolerance tests in PAM is in agreement with previous findings obtained by us and by others [1, 2, 8, 16].

Table 1. *Clinical data in patients with primary myxoedema*

Case	Sex	Age (yrs)	Weight (kg)	% ideal weight	Height (cm)	PBI μg%	Cholesterol mg%	BMR ± %	^{131}I % uptake at 6 and 24 h	Thyroid antibodies Boyden's meth.
1. Loc.	F	47	69	+19	153	3.0	346	−13	4— 3	1: 250000
2. Frat.	F	54	78	+23	159	2.0	296	−18	3— 3	1:2500000
3. De Pian.	F	62	72	+24	149	1.6	220	−20	2— 4	1:2500000
4. De Sim.	F	60	64	+ 8	151	2.5	340	−42	0— 0	1:2500000
5. Cant.	F	49	62	+ 2	158	1.5	320	−14	25—32	1: 250000
6. Bian.	F	48	56	− 6	156	1.5	330	−20	0— 0	1: 25000
7. Di Pao.	F	39	63	+14	154	2.5	320	−15	20—25	1: 250000
8. Nor.	M	46	72	+ 1	168	2.5	322	−12	3— 3	1: 250000
9. Pugl.	M	60	84	+18	169	3.0	280	−27	1— 2	1:2500000
10. Ros.	F	55	62	+ 3	154	2.0	360	−25	1— 2	1:2500000
11. Bud	M	29	73	+ 6	170	1.2	320	−26	3— 3	1:2500000
12. But.	F	46	62	+ 4	156	1.2	340	−38	2— 2	1:2500000

In PAM, plasma insulin levels in the fasting state do not differ significantly from normal. After glucose administration they rise progressively above normal levels reaching a maximum of 217 ± 69 μU/ml at 120′; the differences are significant at 120′.

Plasma glucagon in PAM does not differ from normal in the fasting state and soon after glucose administration, but it is lower than normal at 60′ and 120′ with a significant difference at 60′ min.

Arginine Test (ATT) Table 3

In patients with PAM blood glucose increases slightly more than in normal subjects during the arginine infusion, with a significant difference at 30′, and subsequently falls to levels significantly lower than normal at 90′ and 120′.

Insulin levels are considerably higher than normal throughout the period of observation; the differences are significant at all points from 20′ to 90′.

Plasma glucagon response to arginine in PAM patients is smaller than in normal subjects. The difference is statistically significant at 30′.

Growth hormone response in myxoedema is smaller than normal. The difference is significant at 60′.

Earlier reports summarized by Elrick *et al.* [7] gave contradictory data on glucose tolerance in hypothyroidism. No clear explanation of these discrepancies is apparent; however most of these reports do not concern primary hypothyroidism or do not distinguish primary adult myxoedema from congenital or iatrogenic hypothyroidism, and therefore are not strictly comparable with our data.

The persistence of high insulin levels at 120′ after oral glucose in conjunction with elevated blood glucose levels might be the expression of insulin resistance [3] and/or delayed glucose absorption [14].

The reduced glucagon response to oral glucose in myxoedema is of interest.

Since it is well known that oral administration of glucose is followed by an increase in blood of a material originating from the gut, reacting like glucagon in the immunoassay (enteroglucagon), and K52 antiserum is not specific for pancreatic glucagon, it is likely that material assayed in this test is enteroglucagon. It is possible that the delayed gastric emptying rate, characteristic of myxoedema, may be responsible for a reduced stimulus to the enteric cells producing gut glucagon. For a definite clarification of the question it would be necessary to use in the immunoassay an antibody capable of distinguishing pancreatic from gut glucagon.

1 Glucagon antiserum K 52 was kindly provided by Dr. Heding of Novo Research Institute, Copenhagen, and we wish here to aknowledge the courtesy.

Table 2. *Oral glucose tolerance test in myxoedema and in normal subjects*

	Blood glucose mg%				Insulin μU/ml				Glucagon pg/ml			
PAM patients	0′	30′	60′	120′	0′	30′	60′	120′	0′	30′	60′	120′
1. Loc.	110	176	190	178	11	46	56	144	250	325	275	300
2. Di Pao.	82	96	102	112	—	—	—	—	425	1000	250	325
3. De Sim.	80	152	164	90	16	93	138	104	280	425	275	275
4. Bian.	98	185	172	146	17	120	68	110	130	125	125	275
5. Cant.	82	135	140	121	12	93	84	93	525	225	400	350
6. Frat.	94	154	218	164	16	134	180	500	225	950	575	150
7. De Pian.	98	160	178	154	34	100	96	356	110	225	175	275
Mean	92	151	166	137	17	97	103	217	277	467	296	278
± SEM	± 4.2	± 11.0	± 14.0	± 11.7	± 3.3	± 12.2	± 19.1	± 69	± 56.9	± 135	± 56	± 28
Normals	0′	30′	60′	120′	0′	30′	60′	120′	0′	30′	60′	120′
1. Sec.	94	148	132	90	27	86	100	91	200	950	950	325
2. Gazz.	74	106	95	80	18	50	34	13	350	350	650	800
3. Roc.	75	133	137	142	20	76	98	64	325	750	325	150
4. Domin.	78	97	104	76	12	44	—	36	425	300	1250	300
5. Buzz.	82	106	100	76	24	76	66	50	175	875	225	500
6. Ciot.	96	162	126	100	28	112	104	64	125	450	325	300
7. Fran.	98	211	178	68	16	44	50	50	—	575	1375	—
8. Sech.	95	160	146	72	12	22	50	54	250	125	300	100
Mean	86	140	127	88	19	63	71	52	264	546	675	360
± SEM	± 3.6	± 15.6	± 9.7	± 8.5	± 2.2	± 10.1	± 10.8	± 6.5	± 40	± 103	± 162	± 95
p	NS	NS	< 0.01	< 0.0025	NS	NS	NS	< 0.01	NS	NS	< 0.05	NS

The increase in insulin levels following arginine infusion in PAM is strikingly greater than normal. This confirms that PAM subjects are capable of secreting large amounts of insulin. This response to arginine of PAM subjects differs from that which follows either oral or intravenous [3, 8] glucose in that is very prompt. A similar behaviour has been observed by us in PAM after glucagon administration [3]. The different response of beta cells to glucose and respectively to arginine and glucagon may be explained by the existence of different pathways for glucose-induced and arginine-, or glucagon-induced secretion.

In myxoedema, either glucose metabolism itself or the transmission of the information from the membrane glucose receptor of the beta cell might be slower than normal, causing a selective impairment of the response to glucose.

The increased blood glucose response observed in PAM patients at the end of the arginine infusion is difficult to explain, while the marked fall observed in these subjects at 90′ and 120′ is probably a consequence of the very large output of insulin, overcoming insulin resistance.

Plasma glucagon increase in PAM was significantly smaller than in normal subjects; as the increase of IRG levels after arginine is thought to be due to secretion of pancreatic glucagon (nesidioglucagon) [19] our findings should indicate a reduced alpha cell response to arginine in PAM. As hyperglycaemia and hyperinsulinaemia are known to suppress glucagon secretion, it might be that this mechanism operates in PAM patients during the first phase of the test. On the other hand a reduced glucagon response might contribute to the lower blood glucose levels observed at the end of the test.

In PAM the fall of blood glucose after insulin administration is delayed and the GH response, in agreement with the data published by others [15, 27], is reduced. The fact that GH response to arginine is also significantly lowered suggests that reduction of the hypoglycaemic response to insulin is not the factor causing the impaired GH secretion in the insulin tolerance test. The poor GH secretion in myxoedema is probably due to an impairment in the reactivity of the hypothalamo-hypophysial axis, possibly connected with a metabolic derangement of the hypothalamic centres and/or of the pituitary cells.

The behaviour of GH and glucagon does not seem to explain the reduced glucose utilization observed in previous studies. Therefore another explanation must be found. It very likely that in PAM there is a metabolic disturbance which prevents insulin either from reaching reactive sites or from stimulating glucose utilization.

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Table 3. *Arginine tolerance test in myxoedema and in normal subjects*

	Blood glucose (mg%)								Insulin μU/ml							
PAM patients	− 30′	0′	20′	30′	45′	60′	90′	120′	−30′	0′	20′	30′	45′	60′	90′	120′
1. Bud.	65	64	92	108	96	70	35	50	—	29	182	255	246	96	37	30
2. But.	85	86	106	118	77	65	50	53	40	43	258	228	136	74	58	62
3. Ros.	106	103	148	166	139	87	74	80	70	56	288	376	236	72	70	54
4. Nor.	72	70	98	106	100	85	67	72	13	11	69	79	65	31	12	22
5. De Sim.	83	83	119	127	112	100	66	78	16	40	82	152	116	54	18	10
6. Pugl.	72	72	108	106	88	68	70	62	26	22	260	304	196	90	42	22
Mean	80	79	111	121	102	79	60	66	32	33	189	232	165	69	39	33
± SEM	± 6	± 5.7	± 8.1	± 9.5	± 8.8	± 5.6	± 6.1	± 5.0	±10.4	± 6.5	± 38.9	± 43.3	± 29.3	± 9.7	± 9.2	± 4
Normals	− 30′	0′	20′	30′	45′	60′	90′	120′	−30′	0′	20′	30′	45′	60′	90′	120′
1. Bell.	78	78	93	103	96	89	88	85	25	21	40	58	46	38	24	27
2. Seraf.	85	86	106	112	107	96	90	94	25	26	60	—	49	43	26	25
3. Buz.	84	84	98	94	80	68	82	90	25	24	45	80	44	36	21	20
4. Tamb.	90	89	98	70	—	—	—	—	31	50	62	112	48	37	35	33
5. Gaz.	—	100	114	100	88	70	74	86	28	16	67	73	53	29	18	16
6. Guid.	—	100	114	126	120	95	93	96	—	29	52	92	63	29	20	24
7. Domin.	84	84	98	94	80	68	82	90	12	18	50	68	54	22	20	12
Mean	84	88	103	99	95	81	84	90	24	26	53	75	51	33	23	22
± SEM	± 1.9	± 3.3	± 3.2	± 6.5	± 6.5	± 5.6	± 2.8	± 1.8	± 2.6	± 4.3	± 3.6	± 9.3	± 2.4	± 2.6	± 2.2	± 2.6
p	NS	NS	NS	< 0.05	NS	NS	< 0.005	< 0.001	NS	NS	< 0.025	< 0.005	< 0.0005	< 0.0025	< 0.005	NS

	Glucagon (pg/ml)								Growth hormone (ng/ml)							
PAM patients	− 30′	0′	20′	30′	45′	60′	90′	120′	−30′	0′	20′	30′	45′	60′	90′	120′
1. Bud.	—	—	—	—	—	—	—	—	1.0	1.0	9.0	15.0	15.6	8.5	6.8	4.2
2. But.	—	170	380	440	350	420	380	410	—	0.5	1.2	1.4	4.5	4	2.6	1.5
3. Ros.	100	150	75	150	150	25	25	25	1.2	1.5	1.2	4.5	4.4	9.9	6.6	5.7
4. Nor.	—	—	—	—	—	—	—	—	0.5	0.5	7.5	5.6	5.5	7.2	3.2	0.7
5. De Sim.	25	100	100	25	100	25	100	100	0.5	1.0	0.5	1.5	3.5	0.5	2.7	0.9
6. Pugl.	575	350	350	675	725	375	50	75	0.5	0.5	0.5	0.5	2.8	6.5	4.5	2.5
Mean	233	192	226	322	331	211	138	152	0.7	0.8	3.3	4.7	6.2	6.1	4.4	2.6
± SEM	±172	± 54	± 80	± 83	±142	±108	± 81	± 87	± 0.2	±0.2	± 1.6	± 2.2	± 2.1	± 1.4	± 0.8	± 0.8
Normals	− 30′	0′	20′	30′	45′	60′	90′	120′	−30′	0′	20′	30′	45′	60′	90′	120′
1. Bell.	—	55	55	720	—	480	660	230	—	1.5	1.9	7.5	8.2	9.5	8.4	9.0
2. Seraf.	—	65	485	—	375	180	55	55	0.5	0.5	0.5	6.5	19.6	20.0	9.7	8.3
3. Buz.	—	325	400	500	800	250	175	200	0.5	2.0	9.6	19.2	39.0	36.0	18.9	4.5
4. Tamb.	—	380	1100	880	480	430	430	370	0.5	0.5	0.5	3.4	2.8	2.5	2.0	0.5
5. Gaz.	—	140	350	440	670	220	—	140	0.8	0.5	0.5	1.0	2.0	3.0	0.8	0.5
6. Guid.	—	360	260	760	440	360	60	150	1.5	0.5	4.8	12.3	28.4	22.5	13.5	4.6
7. Domin.	—	425	725	—	425	875	600	175	0.5	0.5	0.5	12.9	16.8	22.2	6.9	2.1
Mean	—	250	496	660	531	399	330	188	0.7	0.8	2.6	8.9	16.6	16.5	8.6	4.3
± SEM		± 59	±129	± 82	± 68	± 90	±110	± 37	± 0.2	±0.3	± 0.8	± 3	± 5.2	± 4.6	± 2.4	± 1.3
p	NS	NS	NS	< 0.05	NS	NS	NS	NS	NS	NS	NS	NS	NS	< 0.05	NS	NS

Table 4. *Insulin tolerance test in myxoedema and in normal subjects*

	Blood glucose (mg%)							Growth hormone (ng/ml)						
PAM patients	−30′	0′	20′	30′	45′	60′	90′	120′	−30′	0′	20′	30′	45′	60′	90′	120′
1. Bud.	65	65	48	40	42	51	69	—	2.0	1.4	1.5	2.6	1.8	3.8	2.7	2.5
2. But.	90	90	50	35	52	48	50	—	—	0.5	1.5	0.5	6.2	12.8	8.5	—
3. Nor.	—	88	50	35	—	30	35	50	—	0.5	0.5	0.5	11	18	13.7	4
4. De Sim.	—	80	52	42	50	52	52	58	—	0.5	0.5	0.5	3.8	19	11.2	4.7
5. Loc.	—	80	72	64	—	60	50	40	—	1.2	0.5	1.5	1.6	4.5	2.5	0.5
6. Pugl.	90	84	56	42	50	50	34	38	2.4	1.3	0.5	0.5	3	8.5	6	3
Mean	81	81	54	43	48	48	48	46	2.2	0.9	0.8	1	4.5	11.1	7.4	2.9
± SEM	± 8.3	± 3.6	± 3.3	± 4.4	± 6	± 4	± 5.2	± 4.6	—	±0.2	± 0.2	± 0.4	± 1.4	± 2.7	± 1.8	± 0.7
Normals	−30′	0′	20′	30′	45′	60′	90′	120′	−30′	0′	20′	30′	45′	60′	90′	120′
1. Lanc.	—	86	34	40	52	62	70	—	—	2.3	11	17.5	45.5	18.3	12.6	—
2. Mald.	—	81	35	32	47	60	68	—	—	0.5	0.5	30	36	44.2	31.6	—
3. Ferr.	74	82	32	32	55	62	66	84	—	4.2	3.5	18.5	27	37	13	5.5
4. Puc.	60	64	38	30	36	50	54	65	—	0.5	0.5	0.5	21	56	48	20
5. Chier.	84	90	34	32	66	72	74	80	1.5	0.5	1.5	6.5	22.	28.5	32.5	2.5
6. Felic.	80	92	42	40	36	58	66	78	—	1	9.5	29	39	22	10.7	2.5
Mean	74	82	36	34	49	61	66	77	1.5	1.5	4.4	17	31.7	34.3	24.2	7.5
± SEM	± 6.4	± 4.0	± 1.3	± 1.8	± 4.7	± 2.9	± 2.7	± 4.1		±0.6	± 1.9	± 4.8	± 4.1	± 5.8	± 2.9	± 3.7
	NS	NS	V 0.0025	V 0.025	NS	V 0.025	V 0.01	0.0025	NS	NS	0.05	V 0.01	V 0.0005	V 0.0025	0.025	NS
p																

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