Brief Notes and Comments

Observations in Hyperthyroidism of Abnormal Glucose Tolerance and Other Traits Related to Diabetes Mellitus

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SUMMARY

Studies were made of glucose tolerance and other characteristics related to diabetes in fifty-one patients with hyperthyroidism. Glucose tolerance compatible with diabetes was present in 57 per cent of patients when toxic and 30 per cent on return to euthyroidism. Histories of family diabetes in both sexes and of heavy babies delivered by the women were obtained more frequently than expected in the general population. Reasons are given to suggest a genetic relation between hyperthyroidism and diabetes. DIABETES *14*:740-44, November 1965.

The prevalence of diabetes mellitus in clinical hyperthyroidism is not known with certainty. Estimates of 2.0 to 3.3 per cent have been given, figures little different from that expected for genetic diabetes in the general population.[1] Since this frequency seemed lower than that encountered on the Medical Service at the Cincinnati General Hospital, studies were made of glucose tolerance in hyperthyroid patients over a three-year period. In addition, observations were made of other traits related to genetic diabetes mellitus.

METHODS

(1) *Patients.* The sample for study included all patients in whom the diagnosis of hyperthyroidism was made by the Medical Service of the Cincinnati General Hospital from 12/1/60 to 11/30/63. There were forty-four women and seven men. The mean age was forty-three years. The distributions of thyroid disease and ages are given in table 1.

(2) *Assessment of thyroid function.* Hyperthyroidism was diagnosed by symptoms, signs, and appropriate tests. The mean weight loss claimed was twenty-five pounds or 16.5 per cent of pretoxic weight. The mean basal metabolic rate (BMR) was +35 per cent (range +5 to +90 per cent in forty-three patients), the mean twenty-four hour thyroidal uptake of radioactive iodine (RAI) 87 per cent (range 43 to 118 per cent in forty-six patients), and the mean serum protein bound iodine (PBI) concentration 13 μg. per cent (range 8.2 to 22.0 μg. per cent in twenty-nine patients).

TABLE 1

Distribution of patients by age and thyroid diagnosis

Age	Graves' disease	Toxic nodular goiter	Total
14-19	6	0	6
20-29	8	0	8
30-39	8	0	8
40-49	5	6	11
50-59	1	7	8
60-69	2	4	6
70-78	0	4	4
Total	30	21	51

Achievement of euthyroidism after treatment was judged mainly by disappearance of thyrotoxic symptoms, gain of weight and appropriate tests. The mean BMR was —7 per cent (range —24 to +12 per cent in sixteen patients), the mean RAI uptake 30 per cent (range 8 to 64 per cent in nineteen patients), and the mean serum PBI concentration 5.3 μg. per cent (range 0.8 to 13.4 μg. per cent in twenty-two patients). Two of the sera analyzed for PBI appeared to be contaminated with iodide. If these are excluded, the mean post-treatment concentration becomes 4.6 μg. per cent (range 0.8 to 8.8 μg. per cent in twenty patients).

(3) *Assessment of carbohydrate tolerance.* In preparation for a GTT the patients were asked to eat two additional slices of bread at each meal for three days prior to testing. Patients receiving treatment for diabetes discontinued insulin twenty-four hours and oral antihyperglycemic drugs seventy-two hours before the tests. One hundred grams of glucose in 300 cc. of citrus-flavored ice water were given by mouth, and venous

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blood obtained prior to and at ½, 1, 2, and 3 hrs. after glucose ingestion for determination of sugar.[2] Results were called compatible with diabetic glucose tolerance if they met the criteria of Fajans and Conn, a 1-hr. value of 160 mg./100 ml. or greater plus a 2-hr. value of 120 mg./100 ml. or greater.[3] Results were called borderline if one of these criteria was met, and normal if neither was met. The results were incomplete in two patients because of inability to cooperate.

GTT's were repeated in forty-four patients in the euthyroid state three to sixteen months after antithyroid treatment (mean 8.8 months). The tests were not repeated in seven subjects because of death in two and loss to follow-up in five.

(4) *History of diabetic diathesis.* Histories were obtained and tabulated concerning diabetes in relatives and, in the patients, pregnancy abnormalities common to the diabetic state.

(5) *Serum cholesterol.* Serum cholesterol was determined in the fasting state when the patients were toxic and after return to euthyroidism.[4]

RESULTS

(1) *Carbohydrate tolerance.* The results of GTT's are shown in table 2. Glucose tolerance consistent with diabetes was found in twenty-nine of fifty-one patients (57 per cent) before, and thirteen of forty-four patients (30 per cent) after, antithyroid treatment. It was more common in older patients with toxic nodular goiter than in those younger with Graves' disease. The occurrence of abnormal glucose tolerance could not be related to the degree of thyrotoxicity.

The patients were divided into four groups according to glucose tolerance.

a. *Previously diagnosed diabetes.* In six patients the diagnosis of diabetes had been made before that of hyperthyroidism. From review of their histories it seemed likely that insulin insufficiency antedated the symptoms of hyperthyroidism by several years. Results of tests performed in five patients later in the euthyroid state remained positive for diabetes.

b. *Newly diagnosed diabetic glucose tolerance.* In twenty-three patients (51 per cent) of forty-five results compatible with diabetes were found wherein there was no previous knowledge of carbohydrate disturbance. Patient 47, who did not have a complete tolerance test, is included in this group because of fasting hyperglycemia. Tests performed later in nineteen patients in the euthyroid state yielded values which were consistent with diabetes in six, borderline in four, and normal in nine.

c. *Borderline diabetic glucose tolerance.* In seven patients the results of the tests were borderline as defined above. Tests performed later in six patients in the euthyroid state yielded values consistent with diabetes in one, borderline in one, and normal in four.

d. *Normal glucose tolerance.* In fifteen patients the tests yielded normal values. Patient 18, in whom the test was incomplete, was placed in this group because the 60-min. glucose value (the only one obtained) was 66 mg./100 ml. Tests performed later in fourteen patients in the euthyroid state gave values consistent with diabetes in one, borderline in two, and normal in eleven.

(2) *Family and obstetric histories.* Seventeen patients (33 per cent) knew of diabetes in an immediate relative. Nine of the patients had Graves' disease and eight toxic nodular goiter. Obstetric histories, presumably reliable, were obtained from forty-two of the forty-four women. Of the forty-two, six claimed never to have been pregnant, and five claimed abortions or still births but no live births. Of the thirty-one remaining women, seven stated they had delivered one infant weighing nine or more pounds, and one woman delivered three babies in this weight range. Three of the eight mothers had, in addition, family histories of diabetes. The prevalence of heavy babies was ten in 103 live births, or 9.7 per cent. This exceeds that of 2.7 per cent for nine pounds or heavier babies observed in 16,012 consecutive live births in the period of observation at the Cincinnati General Hospital.[5] Also, the percentage of mothers delivering heavy babies (26 per cent) is greater than that of 12 per cent reported by Wilkerson and O'Sullivan in their series of 752 unselected pregnancies.[6] No relation between histories suggesting predisposition to diabetes and the occurrence of diabetic glucose tolerance was found in the present patients.

(3) *Serum cholesterol.* The mean serum cholesterol concentrations are shown in table 3. Levels measured in the hyperthyroid state were significantly lower ($P < 0.01$) than those measured in the same patients when euthyroid.

DISCUSSION

In the present study glucose tolerance compatible with that of diabetes was indeed common and exceeded previous estimates. Diabetic values were found in over one half the patients when toxic and in almost one third when euthyroidism had been achieved.

TABLE 2

Historical data and glucose tolerance in hyperthyroidism

	Pt. No.	Age	Sex	F.H. diabetes	9-lb. infant	Glucose tolerance: Hyperthyroid F	½	1	2	3	Euthyroid F	½	1	2	3
Previously diagnosed diabetes	13	76	F	no	NH*	156	300	347	291	269	162	218	264	296	340
	14	70	F	yes	NP	311	346	356	412	402	230	456	556	384	304
	21	75	F	no	AB	107	168	198	217	207					
	28	59	F	no	no	180	277	348	344	307	84	145	174	248	283
	30	58	F	no	AB	270		398	484	505	272	387	410	486	472
	41	48	F	yes	no	164	242	285	336	242	225	295	399	445	368
Newly discovered diabetic glucose tolerance	1	25	F	no	no	71	194	176	126	81	76	112	88	64	61
	2	49	F	no	no	75	149	163	139	135	58	86	104	76	73
	5	68	F	no	AB	80	140	171	222	140	80	120	153	93	76
	8	53	M	no		100	134	163	187	163	83	130	164	96	69
	10	52	F	no	no		165	164	168	76	83	149	170	140	98
	16	69	M	no		95	133	182	177	129	114	188	171	152	122
	20	34	F	yes	no	82	146	178	172	69					
	23	69	F	NH	NH	63	156	221	219	178					
	25	17	F	yes	NP	89	202	211	124	83	61	135	130	103	75
	26	51	F	no	no	84	173	210	185	132					
	27	32	M	yes		71	194	235	143	114	54	154	96	64	68
	29	52	F	no	yes	100	267	330	176	34	102	174	197	98	37
	36	33	F	yes	no	59	186	202	199	115	88	123	133	120	113
	37	19	M	no		90	180	210	183	50	96	131	110	83	60
	38	20	F	yes	no	95	177	197	154	134	84	147	179	183	115
	40	78	F	no	no	95	141	182	146	145	67	129	140	104	98
	42	34	F	no	AB	90	180	173	171	129	90	148	91	56	87
	43	43	F	no	no	107	223	232	174	96	90	204	168	149	97
	44	53	F	yes	yes	77	184	163	165	107	71	133	133	130	67
	45	45	M	yes		64	203	215	146	55	70		189	134	56
	46	47	F	no	no	100	247	286	247	124	97	133	146	100	111
	47	68	F	no	NP	130	204				143	198	222	208	186
	48	41	F	no	yes	101	187	234	200	96					
Borderline diabetic glucose tolerance	22	27	F	no	no	92	170	173	118	75	48	78	100	63	63
	31	45	M	no		83	123	136	140	134	100	92	147	143	116
	32	21	F	no	NH	83	208	188	112	80					
	34	43	M	no		87	167	145	155	154	97	167	208	181	155
	39	60	F	yes	NP	85	139	133	120	110	76	108	75	80	74
	49	28	F	yes	no	115	149	128	128	47	68	126	114	96	54
	50	35	F	no	yes	112	166	188	112	67	74	111	90	90	83
Normal glucose tolerance	3	14	F	no	AB	81	148	114	75	74	61	115	104	62	56
	4	19	F	no	no	64	143	120	118	85	72	92	129	132	108
	6	38	F	no	no	90	134	125	106	102	81	126	113	117	94
	7	27	F	yes	yes	70	137	89	100	61	59	110	95	95	89
	9	47	F	yes	yes	80	77	103	52	113	85	169	160	110	49
	11	19	F	yes	no	77	113	138	116	86	78	108	85	71	63
	12	44	F	no	no	74	103	129	100	79	91	120	109	85	71
	15	14	F	no	NP	83	137	91	94	76	51	105	65	66	53
	17	63	F	yes	AB	71	141	139	115	96	91	152	168	129	109
	18	37	F	no	NP			66			50	95	99	112	40
	19	32	F	no	yes	67	164	126	80	90	63	58	66	51	67
	24	57	F	yes	NH	73	254	95	43						
	33	28	F	no	no	93	130	95	97	98	73	73	83	126	46
	35	45	F	no	yes	94	176	156	112	84	72	125	136	86	66
	51	20	F	yes	no	108	146	100		100	89	104	91	110	111

*NP = no known pregnancy
NH = no history obtained
AB = abortions only

TABLE 3

Serum cholesterol

	Hyperthyroid (N)	Euthyroid (N)
Diabetic GTT	180 ± 44 (21)	251 ± 81 (30)
Normal GTT	178 ± 40 (28)	246 ± 59 (12)
Total	178 ± 60 (49)	255 ± 63 (42)

The reasons for the occurrence of hyperglycemia are not clear. Indeed, some investigators have reported increased glucose utilization[7-8] and increased response to insulin.[9-10] Others have suggested that increased intestinal absorption of glucose,[11] abnormal liver function with decreased hepatic glycogenesis [12-14] and increased glycogenolysis[15] might account for the glucose intolerance.

Some years ago Holst et al. proposed that there was islet cell injury in hyperthyroidism.[16] In line with this, Houssay was able to produce meta-thyroid diabetes in dogs only if they had been subjected to subtotal pancreatectomy.[17] It is conceivable that a similar situation exists in human hyperthyroidism. For example, studies of plasma immunoreactive insulin content in patients with hyperthyroidism and hyperglycemia have revealed levels lower than those expected with the degree of blood sugar elevation.[18-19] In fact, a late response of insulin secretion resembling that of early diabetes was seen.[19] Moreover, diabetic glucose tolerance curves persisted in 30 per cent of the present patients after correction of hyperthyroidism. In contrast, Danowski and collaborators failed to produce glucose intolerance in apparently normal subjects given thirty grains of thyroid daily for nine weeks.[20]

A genetic association between diabetes and hyperthyroidism was proposed earlier by Althausen.[21] The high prevalence of diabetes in close relatives of patients with hyperthyroidism found by Perlman (36 per cent)[22] and observed in the present study (33 per cent) support the concept. These prevalences are greater than that observed by Wilkerson et al.[23] in the general population of Oxford, Massachusetts (18.6 per cent) and compare instead with the 38.6 per cent prevalence of positive family histories for diabetes in the diabetic patients of that community. The description of diabetes and hyperthyroidism in identical twins,[24] the increased prevalence of antithyroid antibodies in patients with diabetes[25] and the increased prevalence, described here, of large babies born to women subsequently developing hyperthyroidism provide further evidence for a possible inherited relationship between diabetes and hyperthyroidism. The evidence must remain suggestive, however, until refined technics in study of genetics become available for clinical application.

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False Elevation of Plasma 17-Hydroxycorticoids in Diabetic Ketosis

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SUMMARY

Plasma corticoids were measured by an acid-fluorescent method and a modification of the Porter-Silber reaction in diabetic patients under good control and in states of poor control including ketoacidosis. In patients with significant ketonemia the plasma ketone bodies may produce a falsely high estimation of adrenal corticoid secretion when measured as Porter-Silber chromogens. Evaporation of the plasma extract, or preferably use of the acid-fluorescent procedure, will obviate such interference. DIABETES *14*:744-45, November 1965.

An elevation in plasma hydroxycorticoids in diabetic ketoacidosis would be anticipated because of adrenal stimulation by this marked stress. Recently, Kruger and co-workers[1] have shown that in association with elevated ketone bodies there may be a false elevation in the 17,21-dihydroxy-20-ketosteroid (Porter-Silber chromogen) values in obese patients subjected to fasting. The substance producing this increase could be removed by evaporation of the organic extract prior to the color reaction. This aberration was not seen when plasma corticoids were measured by a technic using acid-fluorescence. Since blood ketones, even in controlled diabetic patients, may be somewhat higher than in nondiabetic subjects,[2] we have compared plasma levels of the Porter-Silber chromogens and acid-fluorescent steroids on the same plasma sample in diabetics without glycosuria or ketonuria, in patients with ketosis and in those with frank diabetic ketoacidosis.

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TABLE 1

A comparison of plasma acid-fluorescent corticoids and Porter-Silber chromogens* in diabetes

Diagnosis	Porter-Silber chromogens μg./100 ml.	Acid-fluorescent corticoids μg./100 ml.	Ketones μg./ml.
Diabetic acidosis	158.8	41.4	430
	139.0	91.1	311
	63.0	26.1	199
Uncontrolled diabetes with ketosis	89.0	20.0	256
	39.5	20.0	31
	68.8	17.1	51
	73.2	25.0	274
Controlled diabetes	16.7	16.4	2.9
	20.5	21.8	12.8
	15.6	21.8	2.4
	9.5	12.8	8.4
	18.4	23.2	6.7
	6.9	11.8	3.1

*Porter-Silber chromogens measured by the method of Peterson and associates.[4]