Carbohydrate Tolerance in Autoimmune Thyroiditis

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SUMMARY

Glucose tolerance tests were carried out on fifty patients with autoimmune thyroiditis of varying duration and severity. Two were floridly diabetic, and a further six showed diabetic abnormalities of glucose tolerance, giving an over-all incidence of 16 per cent. Diabetics were significantly older than nondiabetics, but the two groups did not differ in terms of duration of thyroid disease or frequency of associated disease of probable autoimmune origin. The prevalence of diabetes in patients with autoimmune thyroiditis appears to be the same as that in the population generally. DIABETES *24*:829-32, September, 1975.

It is well known that diabetes may either precede or follow the onset of hypothyroidism.[1-3] Some workers[4] have maintained that the prevalence of diabetes is increased in asymptomatic atrophic thyroiditis although others have failed to confirm this.[5] Conversely, the prevalence of antithyroid autoantibodies is reported to be increased in diabetes.[6,7] Autoimmune damage to both the thyroid gland and pancreatic islet tissue has long been postulated as a basis for the association of the two diseases. Earlier workers failed to find direct evidence for autoimmune damage to islet tissue. However, such evidence is now forthcoming with the recent finding both of circulating anti-islet antibodies[8,9] and cell-mediated immunity to islet tissue[10] in young insulin-dependent diabetics who suffer additionally from autoimmune endocrinopathy.

This study was carried out in order to determine the prevalence of latent or overt diabetes in a potentially high-risk group of patients suffering from an autoimmune disorder sufficiently severe to produce clinically apparent thyroid disease.

MATERIALS AND METHODS

The patients studied were those in whom autoimmune thyroiditis had been diagnosed on the basis of either (a) the presence of thyroglobulin antibodies in a titer of at least 1 in 2,500 (measured by a modified tanned red cell technic[11]) and/or thyroid microsomal antibodies in a titer of at least 1 in 4 (measured by a complement-fixing method[12]) or (b) where histology was available, the typical features of Hashimoto's disease.

All patients of the Endocrine Clinic, New End Hospital, in whom this diagnosis had been made eighteen months or more before the study were asked to attend the Outpatients Department for preliminary interview. Letters were sent to 102 patients, of whom 60 attended for interview. Fifty patients (forty-five female, five male) agreed to be admitted overnight to hospital at a later date for assessment. Their ages ranged from twenty-eight to seventy-seven years (mean fifty-six years). The known duration of thyroid disease ranged from eighteen months to seventeen and one-half years (mean four years). When these patients were previously investigated at the time of their initial referral, all fifty had thyroid enlargement, twenty-two were hypothyroid, sixteen were euthyroid, and twelve were thyrotoxic. Antibodies to both thyroglobulin and thyroid microsomal fraction were present in thirty-five; one or another of these antibodies was present in thirteen, and two patients were antibody-negative but had histologic changes typical of Hashimoto's disease.

When they came for interview, patients were asked to take a normal carbohydrate intake for at least three days before admission.

Patients were questioned and examined for clinical evidence of diabetes mellitus, pernicious anemia, rheumatoid arthritis, or other autoimmune disease. Following an overnight fast, each patient was given 50 gm. dextrose in 250 ml. water. Venous blood was taken at zero time and half hourly thereafter for two and one-half hours. Whole-blood glucose was estimated by a standard glucose oxidase method.[13] Thyroid status was determined by clinical examination and PBI estimation. Sera were examined for the

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presence of antibodies to thyroid cell, parietal cell, and adrenal cortical cell cytoplasm by a sensitive immunofluorescent technic:[14] thyroglobulin and thyroid microsomal antibody titers were also measured and compared with the values obtained when the diagnosis was first established (results to be reported elsewhere).

RESULTS

The results are shown in table 1.

Thyroid status. At the time of study, forty-three patients were taking L thyroxine 0.1-0.5 mg. per day. All were clinically euthyroid. Their PBI levels fell within our normal range for patients on thyroxine replacement therapy (5-10.5 mg. per cent) in forty cases while three patients (nos. 13, 17, and 29) had slightly elevated values. Of the seven patients not on replacement therapy, three (nos. 2, 23, and 33) were clinically and biochemically hypothyroid, while the others were normal.

TABLE 1

No.	Age	Duration of disease (yr.)	Blood Sugar (mg./100ml.) 0′	30′	60′	90′	120′	150′	LT_4 mg./day	PBI μg. %
1	67	6	100	165	140	120	90	75	0.3	9.2
2	64	17.5	91	145	109	64	64	64	—	3.2
3	50	2	68	77	55	68	77	77	0.2	6.5
4	54	5.5	105	145	136	108	118	112	0.2	5.8
5	68	2	100	145	154	127	91	82	0.2	6.3
6	58	5	81	152	152	95	76	81	0.3	5.9
7	60	5.5	82	136	155	136	55	55	0.5	6.8
8	34	1.5	73	146	109	109	82	55	0.2	3.5
9	64	5.5	100	170	105	80	70	55	0.2	6.1
10	33	4	70	95	80	45	55	65	0.1	5.1
11	53	5.5	73	77	132	118	82	68	0.3	7.6
12	48	2.5	77	118	123	127	82	64	0.1	5.6
13	61	5.5	90	140	140	135	85	60	0.3	10.8
14	47	2	90	70	80	80	80	90	0.3	6.8
15	76	4	80	150	170	160	160	120	0.2	5.1
16	54	4	85	140	155	90	85	60	0.3	9.4
17	55	5	79	105	79	74	58	58	0.5	11.0
18	77	4	74	121	137	127	85	63	0.3	5.4
19	49	4	59	117	84	84	67	50	0.15	3.6
20	43	5	59	59	59	59	67	50	0.3	5.4
21	56	1.5	67	100	83	54	59	59	—	6.5
22	52	3.5	67	100	92	75	83	67	0.3	7.6
23	73	4	185	235	265	305	290	270	—	2.8
24	38	3	57	109	85	72	67	62	0.2	6.9
25	68	4	76	114	124	109	95	81	0.1	7.4
26	50	4	85	115	120	110	75	65	0.4	7.5
27	74	5	78	128	82	96	100	100	0.25	5.3
28	60	2	91	105	105	128	114	91	0.3	8.5
29	51	4	73	123	96	78	59	50	0.5	10.7
30	69	2	80	140	185	170	130	95	0.2	5.1
31	68	14	140	220	290	270	265	240	0.2	5.8
32	30	3.5	65	140	125	75	70	65	0.3	7.2
33	48	4	95	205	180	170	160	145	—	3.0
34	39	3	80	117	100	100	100	75	0.3	6.3
35	46	3.5	80	115	100	80	60	52	—	4.0
36	68	4	61	100	109	78	74	61	0.3	5.6
37	67	1.5	83	124	234	222	170	108	0.3	4.2
38	53	2.5	60	68	55	42	38	55	0.3	5.4
39	54	1.5	63	82	70	48	45	62	0.4	5.1
40	51	2	67	120	96	54	46	67	0.3	9.8
41	64	3.5	65	91	75	75	67	54	0.3	10.4
42	41	3.5	75	170	118	82	62	58	0.5	8.6
43	28	3	68	100	70	67	74	70	—	5.2
44	63	3.5	70	122	115	70	60	65	0.3	9.6
45	71	2.5	80	140	160	137	95	52	0.2	6.2
46	52	2.5	65	120	140	118	115	97	0.3	8.6
47	54	2.5	90	145	180	160	130	100	0.2	7.3
48	58	3.5	70	125	190	192	135	78	—	7.3
49	58	3	68	125	135	117	65	43	0.3	4.3
50	60	2.5	68	100	90	90	70	68	0.2	9.3

Carbohydrate tolerance. Normal glucose tolerance was evidenced by a fasting level not greater than 110 mg./100 ml.; one-hour level not greater than 160 mg./100 ml.; and two-hour level not greater than 120 mg./100 ml.

Two patients (nos. 23 and 31) showed florid diabetic abnormalities. The first had symptoms suggestive of diabetes, although the diagnosis had not previously been made, whereas the second was a known diabetic on chlorpropamide therapy, first diagnosed six years after the onset of hypothyroidism. A further six patients (nos. 15, 30, 33, 37, 47, and 48) showed elevated glucose levels at one hour and two hours. One of these (no. 33) was found to be diabetic three years after the diagnosis of thyroid disease and was receiving chlorpropamide therapy. Another patient (no. 37) was found to have a diabetic glucose tolerance curve when the original thyroid investigations were carried out. The remaining four patients were not previously known to be diabetic.

Twelve (29 per cent) of forty-two nondiabetic patients gave a history of diabetes mellitus in a first-degree relative; such a history was elicited from only one diabetic patient.

Two of three hypothyroid patients (nos. 23 and 33) were diabetic, and mean PBI level in diabetics was lower than in nondiabetics, though this was not significant. The two groups did not differ in terms of known duration of thyroid disease, but diabetics were significantly older (table 2).

Pernicious anemia was present in three patients, rheumatoid arthritis in one, and Sjögren's syndrome in one; none of these were diabetic.

It was possible to demonstrate thyroid microsomal antibodies by immunofluorescence in the sera of all patients. Parietal cell antibodies were present in eleven nondiabetic and two diabetic sera, whereas adrenal antibodies were found in only one patient who was nondiabetic.

DISCUSSION

An early report[1] of a patient who developed hypothyroidism four years after the onset of Addison's disease and diabetes mellitus was followed by a description[3] of fifteen cases of primary adrenal and thyroid failure, ten with coexisting diabetes. Several workers[2,3] had suggested that a basic abnormality of immune mechanisms might account for the coexistence of these and other endocrine disorders, such as primary gonadal failure and primary hypoparathyroidism in which organ-specific autoantibodies to some endocrine glands could be demonstrated.

TABLE 2

Patients (no.)	Age (yr.) mean (S.D.)	Duration of thyroid disease (yr.) mean (S.D.)	PBI μg. per cent mean (S.D.)
Diabetic (8)	64.1 (9.8)	4.2 (4.1)	5.3 (2.2)
Nondiabetic (42)	54.0 (11.7)	3.9 (2.5)	6.9 (2.1)
	P <0.01	N.S.	N.S.

Bastenie et al.[4] studied a hospital population of patients with asymptomatic thyroiditis as evidenced by the presence of circulating antithyroid antibodies; patients with overt thyroid disease, including goiter, were excluded. They reported latent or clinical diabetes in 39 per cent of antibody-positive patients and in 24 per cent of antibody-negative age-matched controls. Mulhern et al.[5] reported diabetes in only five of 170 patients with Hashimoto's disease, a frequency less than that found in two groups of matched controls. However, the criteria on which the diagnosis of diabetes was based are not stated. Irvine et al.[6] looked for evidence of autoimmune endocrinopathy in diabetic patients. Prevalence of thyroid microsomal and gastric parietal cell antibodies was significantly increased. These findings were confirmed by Nerup and Binder,[7] who also found a correlation between the prevalence of circulating autoantibodies and duration of diabetes; however, they were unable to detect antibodies to islet tissue to support their concept of an autoimmune basis for some cases of diabetes.

Two groups of workers[8,9] have recently succeeded in demonstrating such antibodies in the sera of certain diabetics. MacCuish et al.[9] found that five of twenty juvenile-onset insulin-dependent diabetics with coexisting Addison's disease had circulating anti-islet antibodies, whereas other diabetic patients, including a juvenile-onset insulin-dependent group who had circulating antithyroid and antigastric antibodies, were negative for anti-islet antibodies. Thirteen of 171 patients studied by Bottazzo et al.[8] had circulating anti-islet antibodies. Eight of these had antiadrenal antibodies also, and five had definite or probable Addison's disease.

The prevalence of diabetes in the study reported here is the same as that in the population generally.[15] An earlier study in this group showed no impairment of adrenal function.[16] It is possible that steroid deficiency consequent to primary autoimmune adrenal disease may facilitate the subsequent development of widespread autoimmune endocrinopathy. Thus, there may be two groups of patients with autoimmune thyroiditis. In one group, thyroid disease occurs early in adult life, associated with idiopathic Addison's dis-

ease, autoimmune diabetes mellitus, and possibly other autoimmune endocrinopathy. In the second group, thyroid disease becomes manifest generally in the fifth and sixth decades, adrenal disease is not found, and diabetes is no commoner than would be expected in the general population.

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