Age-related Glucose Intolerance in Hyperthyroid Patients

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SUMMARY

In an attempt to study age-related metabolic abnormalities, glucose intolerance and serum insulin were examined in normal subjects and hyperthyroid patients. For comparison, serum concentrations of thyroxine (T_4), triiodothyronine (T_3), and total cholesterol were also measured in normal subjects and hyperthyroid patients.

Although serum T_4 concentration remained unchanged, serum T_3 concentration decreased significantly in an elderly group of normal subjects. Similarly, serum T_4 did not change with age and serum T_3 decreased slightly but progressively with age in hyperthyroid patients. In addition, serum total cholesterol concentration increased progressively with age in normal subjects.

Oral glucose tolerance decreased with age in normal subjects despite the same timing, peak level attained, and total magnitude of insulin response for old and young subjects. Although the severity of hyperthyroidism decreases with age, age-related glucose intolerance was much more apparent in hyperthyroid patients because of the age-related decrease of basal concentration, the peak level attained, and the total magnitude of insulin response. It is suggested that age-related glucose intolerance is magnified by the hyperthyroid state. DIABETES *27*:543-49, May, 1978.

Graves's disease is characterized by an abnormally high concentration of glucose in the blood and, frequently, by glycosuria during the course of an oral glucose "tolerance" test.[1-3] Reports on the pattern of insulin secretion during this decreased glucose tolerance are controversial: increased,[4,5] normal,[3] and decreased[6,7] insulin response to insulinogenic stimuli have all been reported.

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Population studies confirm the finding that average blood glucose levels in the fasting state increase with age.[8-10] Although the order of magnitude of the increase may be considered of questionable clinical significance in normal subjects, the small change in blood glucose levels with advancing years is magnified, to a considerable extent, in conditions of glucose challenge and steroid administration.[11]

On the basis of these findings, it can be speculated that varying effects of insulin secretion in hyperthyroid patients are attributable to age-related changes in the patients studied. However, there have been few investigations carried out in a sufficient number of patients to allow statistical analysis of these age-related variations. The purpose of the present study is to contribute to a better assessment of insulin and glucose responses to oral glucose administration in hyperthyroid patients of different ages.

MATERIALS AND METHODS

The height and body weight of all the normal subjects and hyperthyroid patients were measured and the ideal body weight was calculated. The normal subjects were healthy volunteers. None of the normal subjects or hyperthyroid subjects was obese. The diagnosis of hyperthyroidism or hypothyroidism was established on clinical grounds and by conventional thyroid function tests, including thyroidal radioiodine uptake, serum concentrations of thyroxine (T_4) and triiodothyronine (T_3), and measurement of serum thyroid-stimulating hormone (TSH) after administration of thyrotropin-releasing hormone (TRH). Serum cholesterol concentration was determined by the AutoAnalyzer technique. Serum T_4, T_3, and TSH were determined by radioimmunoassay with commercially available kits.

The normal subjects and hyperthyroid patients were asked to take a constant diet in regard to calories and carbohydrates for at least seven days before the test. An oral glucose tolerance test was performed in 86 hyperthyroid patients and 37 normal subjects. The test was started between 8 and 9 a.m. after an overnight fast. Venous blood samples were obtained before and 30, 60, 90, 120, and 180 minutes after an ingestion of 50 gm. glucose. The blood was divided into two portions, one of which was analyzed promptly for glucose, while the serum was separated from the other as soon as possible and frozen until an insulin assay could be performed. Whole blood glucose was measured by AutoAnalyzer, and serum immunoreactive insulin was measured by a two-antibody technique.

RESULTS

Blood Glucose and Serum Insulin in Hyperthyroid Patients of Different Ages After Oral Administration of Glucose

Eighty-six (86) patients of different ages were divided into five groups according to age (H-A group: 10 to 20 years, H-B group: 21 to 30 years, H-C group: 31 to 40 years, H-D group: 41 to 50 years, and H-E group: more than 51 years) (table 1 and figure 1). Fasting blood glucose was 84 mg./100 ml. in the H-A group, and this level increased gradually with age except in the H-D group. Two additional age-related changes were found after administration of 50 gm. glucose orally: First, the maximal value of blood glucose was 150 mg./100 ml. in the H-A group, and this maximal value increased progressively with age. The difference between the H-A and H-E groups was statistically significant ($p < 0.02$). The maximal increase of blood glucose appeared 30 minutes after administration of glucose in the H-A, H-B, H-C, and H-D groups, but it appeared 60 minutes after administration of glucose in H-E group. Blood glucose at 180 minutes after administration of glucose was about 70 to 80 mg./100 ml. in all groups. Second, when glucose response was expressed as the area above fasting level (table 1), the area increased progressively with age. The difference between the H-A and H-E groups was statistically significant ($p < 0.025$).

The fasting serum insulin level was 13.8 μU./ml. in the H-A group, and the value decreased gradually with age (table 1 and figure 1). The decrease was statistically significant between the H-A and H-E groups. As in the case of the blood glucose level, the maximal increase of serum insulin was found 30 minutes after administration of 50 gm. glucose orally in the H-A, H-B, and H-C groups. In contrast, the maximal insulin level was found 60 minutes after administration in the H-D and H-E groups. In addition, the maximal value of serum insulin decreased progressively with age. The difference between the H-A and H-E groups was statistically significant ($p < 0.05$). This was also true when insulin was expressed as the area above fasting level for 180 minutes. The difference between the H-A and H-E groups was again

TABLE 1

Effects of aging on blood glucose and serum insulin concentrations after administration of 50 gm. glucose orally

Group	Age (yr.)	Number of subjects	Glucose fasting mg./100 ml.	Insulin, fasting μU./ml.	∫Glucose area above fasting	∫Insulin area above fasting	$\frac{\int \text{Insulin area}}{\int \text{Glucose area}}$
Control							
C-B	21-30	15	80.0 ± 2.3*	10.4 ± 1.3	72.6 ± 8.1	127.8 ± 13.9	2.06 ± 0.34
C-E	> 51	22	82.1 ± 2.6	9.7 ± 0.8	155.6 ± 16.1	152.5 ± 20.5	1.08 ± 0.17
Hyperthyroid							
H-A	10-20	13	84.2 ± 3.3	13.8 ± 1.8	150.5 ± 24.8	175.0 ± 27.9	1.38 ± 0.21
H-B	21-30	23	84.6 ± 2.0	11.3 ± 1.3	164.2 ± 15.8	171.1 ± 18.3	1.28 ± 0.19
H-C	31-40	13	87.2 ± 4.1	10.7 ± 1.7	200.4 ± 18.5	142.7 ± 32.6	0.80 ± 0.17
H-D	41-50	22	84.8 ± 2.6	8.8 ± 1.3	220.1 ± 21.6	145.6 ± 17.4	0.78 ± 0.10
H-E	> 51	15	92.1 ± 4.0	8.0 ± 0.9	238.2 ± 22.8	110.6 ± 14.1	0.53 ± 0.07
Statistical analysis							
C-B vs. C-E			N.S.†	N.S.	$p < 0.001$	N.S.	$p < 0.01$
C-B vs. H-B			N.S.	N.S.	$p < 0.001$	N.S.	$p < 0.05$
C-E vs. H-E			$p < 0.05$	N.S.	$p < 0.005$	N.S.	$p < 0.025$
H-A vs. H-E			N.S.	$p < 0.01$	$p < 0.025$	$p < 0.05$	$p < 0.001$
H-B vs. H-E			N.S.	N.S.	$p < 0.025$	$p < 0.05$	$p < 0.005$

*Mean ± S.E.
†Not significant.

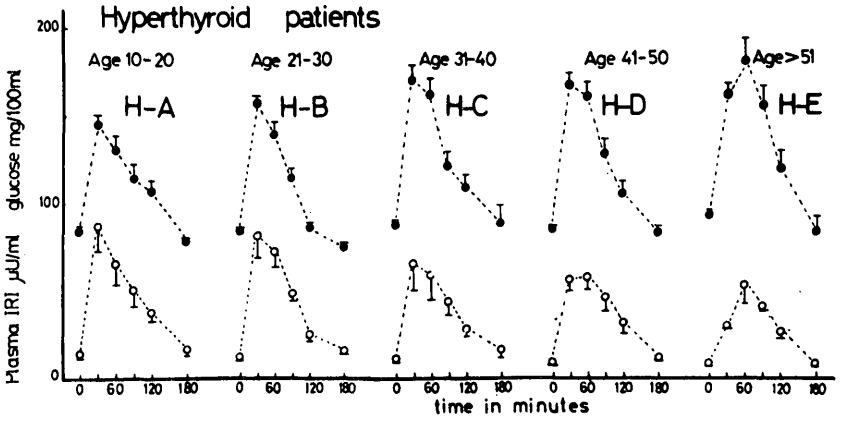

FIGURE 1

Blood glucose and serum insulin concentrations after oral administration of 50 gm. glucose in hyperthyroid patients. Solid circles indicate glucose, and open circles indicate insulin. Circles and vertical lines indicate Means ± S.E. calculated in from 13 to 23 patients. Statistical analysis: Maximal blood glucose of H-A vs. H-E, $p < 0.02$; maximal serum insulin of H-A vs. H-E, $p < 0.05$.

statistically significant ($p < 0.05$). Serum insulin concentration was comparable to the fasting value in each group 180 minutes after administration of glucose.

Finally, $\int$insulin/$\int$glucose was calculated (table 1). Since glucose increased with age and insulin decreased with age, $\int$insulin/$\int$glucose decreased progressively with age.

Blood Glucose and Serum Insulin Concentrations in Normal Subjects of Different Ages After Oral Administration of Glucose

In two groups (C-B group: 15 subjects, 21 to 30 years; and C-E group: 22 subjects older than 51 years), blood glucose and serum insulin concentrations were studied before and after administration of 50 gm. glucose orally. The age range in the C-E group was 51 to 78 years and the mean ± S.E. was 60.4 ± 3.4 years. These values were comparable to those found in the older hyperthyroid patients (H-E) (51 to 71 years, 57.1 ± 1.2 years). The fasting blood glucose level was the same in the young and the older groups. The maximal blood glucose concentration was found at 30 minutes after glucose administration in both groups. As compared with the C-B group, the maximal blood glucose concentration in the C-E group increased significantly ($p < 0.05$). When the glucose response was expressed as the area above the fasting level, the difference between the C-B and C-E groups was statistically significant ($p < 0.001$).

An increase of insulin was observed 30 minutes after oral administration of 50 gm. glucose, with a peak value being achieved at 30 minutes (figure 2). In the elder subjects (C-E group), the timing, the peak value attained, and the area above fasting level in insulin response were indistinguishable from those in the young subjects (C-B group).

Finally, $\int$insulin/$\int$glucose was calculated (table 1). As expected, $\int$insulin/$\int$glucose was significantly less in the C-E group than in the C-B group.

Alterations of Serum Thyroid Hormones and Cholesterol Concentrations in Normal Subjects and Hyperthyroid Patients with Age

Serum T_4 and T_3 concentrations were measured in 22 normal subjects (table 2). Serum T_4 concentration was the same in both young (C-B group) and older subjects (C-E group). In contrast, serum T_3 concentration decreased slightly but significantly in older

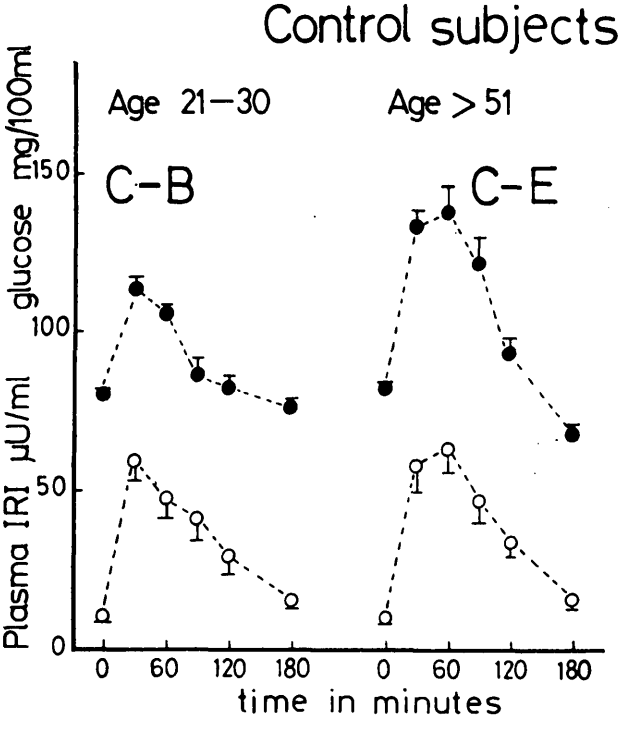

FIG. 2. Blood glucose and serum insulin concentrations in normal subjects. Solid circles indicate glucose, and open circles indicate insulin. Circles and vertical lines indicate Means ± S.E. calculated in from 15 to 22 subjects. Statistical analysis: Maximal blood glucose of C-B vs. C-E, $p < 0.05$.

TABLE 2

Effects of aging on serum thyroid hormone and cholesterol concentrations in normal subjects and hyperthyroid patients

Group	Age (years)	Number of subjects	T_4 μg./100 ml.	T_3 ng./100 ml.	Cholesterol mg./100 ml.
Control					
C-B	21-30	9	7.5 ± 0.5*	114.9 ± 7.0	172.2 ± 8.2
C-C	31-40	21			177.9 ± 8.2
C-D	41-50	20			197.1 ± 9.0
C-E	> 51	13	8.8 ± 0.6	87.3 ± 6.8	202.1 ± 12.5
Hyperthyroid					
H-A	10-20	13	19.8 ± 2.1	414.1 ± 84.4	143.7 ± 8.6
H-B	21-30	23	22.3 ± 1.2	633.7 ± 46.8	138.5 ± 5.7
H-C	31-40	13	24.5 ± 1.2	600.6 ± 69.8	126.4 ± 8.1
H-D	41-50	22	21.6 ± 1.4	445.6 ± 42.3	145.3 ± 6.3
H-E	> 51	15	23.3 ± 2.3	512.9 ± 66.3	139.8 ± 9.8
Statistical analysis					
C-B vs. C-E			N.S.†	$p < 0.05$	$p < 0.05$
H-B vs. H-D			N.S.	$p < 0.05$	N.S.

*Mean ± S.E.
†Not significant.

subjects (C-E group). An additional 41 subjects were examined to detect age-related changes of serum cholesterol. As indicated in table 2, serum cholesterol concentration increased progressively with age. The difference in cholesterol concentration between C-B and C-E was statistically significant ($p < 0.05$).

Serum concentrations of T_4, T_3, and cholesterol were measured in the 86 hyperthyroid patients. As expected, serum T_4 was high in all of these, and its value was maximal at 31 to 40 years (H-C group). It decreased slightly thereafter, but the difference was not statistically significant. Similarly, serum T_3 concentration was high in all hyperthyroid patients, and its value was maximal at 21 to 30 years (H-B group). Thereafter it decreased progressively with age, except in the H-E group, in which the T_3 value was slightly higher than that of the H-D group. The difference in T_3 concentration between the H-B and H-D groups was statistically significant ($p < 0.05$). On the other hand, serum cholesterol concentration did not show significant alteration with age.

Relation Between Serum Triiodothyronine and Cholesterol Concentrations in Hypothyroid Patients, Normal Subjects, and Hyperthyroid Patients

Relationship between serum T_3 and cholesterol concentrations was studied in 39 hypothyroid patients, 57 normal subjects, and 65 hyperthyroid patients. As shown in figure 3, serum cholesterol concentration increased markedly and progressively with decreasing concentration of T_3 when T_3 concentration was below normal (less than 80 ng./100 ml.). Within the normal range of T_3 (80 to 180 ng./100 ml.), an inverse relation was found between the T_3 and cholesterol concentrations. However, when serum T_3 concentration increased above normal (more than 180 ng./100 ml.), serum cholesterol concentration was depressed maximally regardless of whether the hyperthyroid patients were young or old.

DISCUSSION

As a result of increased metabolic processes, increases of intestinal glucose absorption,[12-14] peripheral glucose utilization,[15,16] hepatic glycogenolysis,[17,18] and insulin degradation[19] are all found in hyperthyroid patients. These factors are undoubtedly more or less related to impaired oral glucose tolerance, which is commonly observed in hyperthyroid patients. However, the explanations offered for impairment of glucose tolerance are contradictory. For instance, increased,[4,5] normal,[3] and decreased[6,7] insulin secretions are all reported as occurring with glucose intolerance.

It has been shown that small changes in the fasting blood glucose level with advancing years are magnified to a considerable extent by a glucose challenge and steroid administration.[11] Since hyperglycemia is produced by both Cushing's syndrome and hyperthyroidism, we speculated that the varying results seen on insulin secretion are attributable to age-related alterations. To test this hypothesis, we studied the age-related change of glucose intolerance as well as other aspects of metabolism.

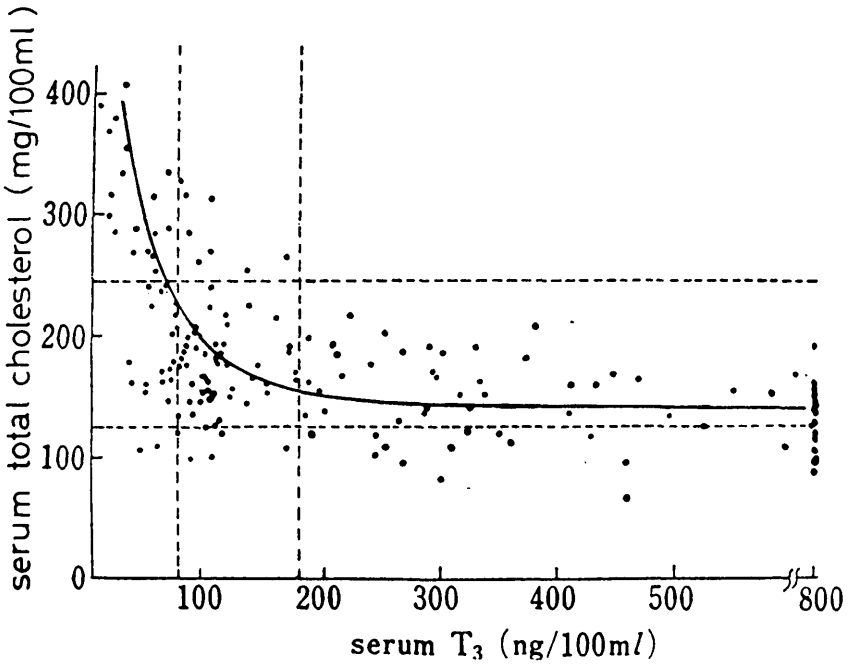

FIGURE 3

Relationship between serum T_3 concentration and serum total cholesterol concentration. Dashed lines indicate normal range.

In agreement with the previous reports,[20-23] our present study clearly indicates that serum T_3 decreases significantly in older subjects. Possible mechanisms are decreased thyroid secretion, decreased peripheral T_4-to-T_3 conversion, increased T_3 distribution volume, and increased rate of T_3 metabolism, or a combination of these factors. Nomura et al.,[24] in a recent paper, suggest that a decrease in T_4-to-T_3 conversion is the predominant cause of the nonthyroidal low T_3 syndrome. Kinetic analysis[25] of T_4 and T_3 suggests that low serum T_3 in older subjects is due to decreased peripheral conversion of T_4 to T_3. Since about 70 per cent of serum T_3 is synthesized in peripheral tissues through monodeiodination of T_4,[26] and since serum T_4 concentration is the same in young and older subjects,[20,21,23] it seems that the monodeiodinating activity of peripheral tissues decreases progressively with age. The age-related increase of serum cholesterol found in our work and others'[27,28] is also of interest. Since serum T_4, as judged by protein-bound iodine (PBI), influences cholesterol metabolism,[29] and since T_3 is three to five times more metabolically active than T_4, we studied the relationship between serum cholesterol and T_3 concentrations. As expected, serum cholesterol concentration is inversely correlated with serum T_3 concentration when serum T_3 concentration is below normal. It seems, therefore, that a progressive decrease of serum T_3 with age is one of the factors responsible for a progressive increase of serum cholesterol. It is further found that glucose tolerance declines with age despite the same timing, peak level attained, and total magnitude of insulin response in the old and young subjects. As already mentioned by others,[10,30] it seems difficult to relate this glucose intolerance to a deficiency of insulin release as measured by radioimmunoassay. However, since a deficiency of the acute phase of insulin secretion may have contributed to glucose intolerance in adult-onset diabetes, it is possible that impairment of the beta cell's acute response to glucose is responsible for age-related glucose intolerance. This possibility is not supported by the study of Palmer and Ensinck,[30] who found a deterioration of acute glucose disposal rate in older subjects despite the same timing and magnitude of acute insulin response for the old and young subjects. Thus, these glucose-insulin relationships suggest the age-related insensitivity of peripheral tissues to insulin, if immunologically determined insulin is biologically active. The exact sites and mechanisms of this insulin insensitivity remain to be determined.

Age-related metabolic abnormalities are also found in hyperthyroid patients. First, severity of hyperthyroidism, as judged by serum T_3 concentration, decreases significantly with age. Although T_3 is elevated above normal, no age-related alteration of serum cholesterol is found. Second, as was found in a previous study[5] on hyperthyroid patients and control sub-

jects matched for age, sex, and degree of obesity, the mean fasting blood glucose level is elevated in hyperthyroid patients. Third, age-related glucose intolerance is apparently magnified in hyperthyroid patients, as evidenced by an increase of peak level and area above fasting level in blood glucose after administration of 50 gm. glucose. This glucose intolerance is associated with a progressive decrease of the peak level and total magnitude of insulin response. As a result, age-related change in $\int$insulin/$\int$glucose is increased in hyperthyroid patients. It should be noted that insulin secretion, expressed as the peak value of insulin, is higher in young hyperthyroid patients than in young controls. If increased degradation of insulin is taken into account, it seems that insulin secretion is increased in young hyperthyroid patients. Thus, the contradictory results previously reported may possibly be explained on the basis of our present findings. For instance, one may find an increase of insulin secretion and elevation of blood glucose when young hyperthyroid patients are used as the representatives of hyperthyroidism; on the other hand, one may find an elevation of glucose and a decrease of insulin secretion in the older patients.

The exact mechanism by which hyperthyroidism produces an age-related depression of insulin secretion and increases an age-related glucose intolerance is not known at present. Since the activity of converting T_4 to T_3 in peripheral tissues declines with age, our present findings provide a basis for further investigations on age-related metabolic impairment of peripheral tissues in man.

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