Effects of Antithyroid Drug Therapy on Blood Glucose, Serum Insulin, and Insulin Binding to Red Blood Cells in Hyperthyroid Patients of Different Ages

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The mechanism of glucose intolerance in thyrotoxicosis was investigated in 119 patients with Graves's disease with careful consideration of the age-related deterioration of glucose tolerance. Before and after treatment of thyrotoxicosis with antithyroid drug, changes of blood glucose (BG) and serum immunoreactive insulin (IRI) in response to 50 g oral glucose tolerance test (OGTT) and insulin binding to red blood cell (RBC) were evaluated. In control subjects, the ΣIRI/ΣBG ratio after 50-g OGTT decreased progressively with age without significant change in absolute ΣIRI value, suggesting the occurrence of age-related insulin resistance. Glucose intolerance was much more apparent in hyperthyroid patients because of age-related relative decrease of insulin secretion. Such a decrease of insulin secretion was not found in age-matched postgastrectomy patients with a similar degree of hyperglycemia, however. Maximal binding of labeled insulin and number of insulin receptors of RBC were decreased in old patients but binding affinity was unchanged. Elevation of BG was partially suppressed when serum thyroxine (T_4) and triiodothyronine (T_3) were reduced to moderately supernormal levels, whereas ΣBG, ΣIRI, ΣIRI/ΣBG ratio, and insulin binding to RBC were all returned to normal when normal serum thyroid hormone concentration was maintained. Our data indicate that insufficient insulin secretion and reduced insulin action at the target cell are responsible, at least in large part, for age-related glucose intolerance in hyperthyroid patients. DIABETES CARE 1985; 8:161–68.

Disorders of carbohydrate metabolism in patients with Graves's disease have been recognized for a long time.[1-3] The clinical syndrome of early-phase hyperglycemia and glycosuria, weight loss, abnormalities in glucose tolerance test (GTT), and tendency toward ketosis during a short period of fasting[4] resemble, superficially at least, the manifestations of diabetes mellitus.[5] In view of the frequency of transient alimentary glycosuria and mild fasting hyperglycemia in patients with Graves's disease, the diagnosis of diabetes mellitus with hyperthyroidism may sometimes be considered.[6] Our previous study[7] indicates that the elevation of blood glucose (BG) levels with advancing age was relatively more in the hyperthyroid state. It was further shown that age-related glucose intolerance was due to age-related decrease of basal concentration, the peak level attained, and the total magnitude of insulin secretion.

Although sufficient experiments are not available at present, it is generally believed that in some patients a high BG response due to ingestion of glucose might quickly be reversed to normal after treatment of hyperthyroidism, whereas in other patients, a less abnormally high response might still remain above normal during treatment.[8,9] However, it is not known whether abnormal glucose tolerance is quickly normalized only in young hyperthyroid patients with sufficient insulin secretion or whether normalization is also quickly produced even in old hyperthyroid patients because of improvement of insulin secretion. It is also not known whether a possible age-related decrease of insulin binding to the cell is responsible, at least in part, for age-related decrease of glucose tolerance in patients with Graves's disease.

To shed some light on these problems, our present study was carried out in a sufficient number of hyperthyroid patients before and during appropriate treatment with antithyroid drug. For comparison, the study was also made in normal subjects and in patients with early-phase hyperglycemia due to gastrectomy.

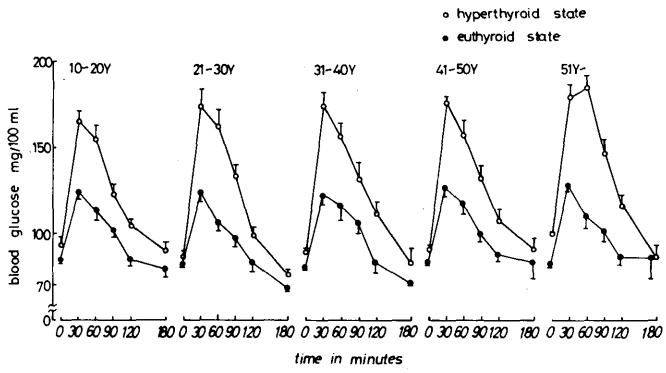

FIG. 1. *Age-related glucose intolerance in patients with Graves's disease before (○) and after (●) appropriate treatment with antithyroid drug. Oral glucose (50 g) was administered at 0 time. Circles and horizontal lines indicate mean ± SE.*

MATERIALS AND METHODS

One hundred nineteen women with hyperthyroidism, 112 normal women, and 12 women with early-phase hyperglycemia due to gastrectomy were evaluated in the present study. All were nonobese (within 10% of ideal body weight). The diagnosis of hyper- or euthyroidism was established on clinical background and by thyroid function test including radioiodine uptake, serum T_4, T_3, and thyroid-stimulating hormone (TSH) measurement by commercially available radioimmunoassay kits. Normal ranges for T_4, T_3, and TSH concentrations were 4.5–11.5 μg/dl, 90–180 ng/dl, and 0–10 μU/ml, respectively.

All subjects and patients were asked to follow a standard diet (2245 cal; 75 g protein, 250 g carbohydrate, and 105 g fat) for at least 7 days before the 50-g OGTT. OGTT was started between 8 and 9 a.m. after overnight fasting. Venous blood samples were obtained before and 30, 60, 90, 120, and 180 min after ingestion of 50 g glucose. 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 measurement could be performed. Whole BG was measured by AutoAnalyzer, Dainabot, and serum immunoreactive insulin (IRI) was measured by commercially available kit.

Insulin receptor assay for human erythrocyte was done by the method of Gambhir et al.[10] In brief, porcine monocomponent insulin (Novo Research Institute, Copenhagen, Denmark) was radioiodinated with Na-^{125}I by chloramine-T method and monomer insulin peak was separated by Sephadex G-50 column chromatography. The erythrocyte pellet was separated from fresh, heparinized blood by the Hypaque-Ficoll method and resuspended in the buffer to obtain 4.0×10^9 cells/ml. Reticulocyte count was done. A 400-μl cell suspension was incubated with a tracer amount of ^{125}I-insulin and various amounts of unlabeled insulin at 15°C for 2 h. After incubation, the cell pellet was separated by centrifugation and its radioactivity was counted. The percentage of specific binding was determined by subtracting the nonspecific binding, ^{125}I-insulin bound in the presence of 1×10^5 ng/ml unlabeled insulin, from the total binding.

Among the multivariate procedures described by Cupples et al.,[11] Holling's T^2 test was used to compare two groups. A P-value <0.05 was considered statistically significant.

RESULTS

Blood glucose and serum insulin in untreated hyperthyroid patients of different ages after oral administration of glucose. One hundred thirteen untreated hyperthyroid patients of different ages were *divided according to age into five groups: H-A group, 10–20* yr; *H-B* group, *21–30* yr; *H-C* group, 31–40 yr; *H-D* group, 41–50 yr; and H-E group; ≥51 yr (Figure 1).

Two age-related changes were found after oral administration of 50 g glucose. First, the maximal value of BG increased progressively with age (H-A versus H-E, $P < 0.05$). The maximal increase of BG appeared 30 min after administration of glucose in patients <50 yr (H-A, H-B, H-C, and H-D groups); whereas, it appeared at 60 min in those ≥51 yr (H-E group). Second, when glucose response was expressed as the area above fasting level (ΣBG)(Table 1), it increased progressively with age. The difference between the H-A and H-E groups was statistically significant ($P < 0.05$).

Fasting serum IRI level decreased gradually with age until 30 yr. As in the case of the BG level, the maximal increase of serum IRI was found 30 min after oral administration of glucose in patients <50 yr, whereas it appeared at 60 min in those ≥51 yr. In addition, the maximal value of IRI decreased progressively with age until 50 yr. The difference between the H-A and H-C groups was statistically significant. Except for the H-E group, age-related decrease of IRI was found when IRI was expressed as the area above fasting level (ΣIRI)(Table 1). The difference between the H-A and H-C groups was statistically significant. Finally, ΣIRI/ΣBG ratio was calculated (Table 1). Except for the H-D group, the ratio decreased progressively with age (H-A versus H-C, $P < 0.005$).

Blood glucose and serum insulin in treated hyperthyroid patients with euthyroidism after oral administration of glucose. BG and serum IRI were measured again in 113 patients about 3 mo after initiation of treatment. All patients received methima-

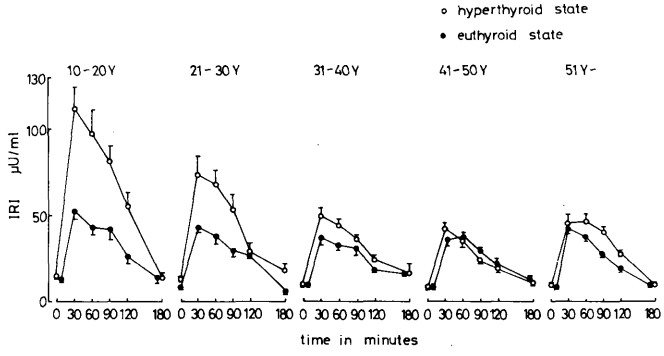

FIG. 2. *Insulin secretion in response to glucose before (○) and after (●) appropriate treatment with antithyroid drug. Oral glucose (50 g) was administered at 0 time. Circles and horizontal lines indicate mean ± SE.*

TABLE 1
Effect of aging on blood glucose (BG) and serum IRI concentration after oral administration of 50 g glucose

Group	Age	No. of subjects	Serum T_4 (μg/dl)*	Serum T_3 (ng/dl)	Fasting BG (mg/ml)	Peak BG (mg/ml)	Fasting IRI (μU/ml)	Peak IRI (μU/ml)	ΣBG	ΣIRI	ΣIRI/ΣBG
Control subjects											
C-A	10–20	12	7.4 ± 0.9	118 ± 1	78 ± 3	107 ± 6	9 ± 1	37 ± 6	84 ± 16	107 ± 17	1.40 ± 0.24
C-B	21–30	10	7.0 ± 0.8	115 ± 11	80 ± 3	116 ± 8	8 ± 1	43 ± 6	111 ± 17	119 ± 22	1.38 ± 0.22
C-C	31–40	26	7.8 ± 0.4	128 ± 9	83 ± 2	128 ± 5	10 ± 1	41 ± 4	147 ± 17	110 ± 11	0.93 ± 0.12
C-D	41–50	29	7.6 ± 0.5	117 ± 7	82 ± 2	126 ± 5	8 ± 1	38 ± 4	140 ± 18	96 ± 12	0.85 ± 0.11
C-E	≥51	35	7.7 ± 0.6	130 ± 12	87 ± 3	135 ± 5	7 ± 1	37 ± 4	166 ± 15	101 ± 12	0.73 ± 0.09
Hyperthyroid patients before treatment											
H-A	10–20	16	17.3 ± 0.9	406 ± 44	94 ± 3	165 ± 6	15 ± 2	112 ± 12	159 ± 16	262 ± 30	1.42 ± 0.20
H-B	21–30	16	18.0 ± 0.9	550 ± 31	88 ± 3	173 ± 10	13 ± 1	73 ± 12	182 ± 13	146 ± 24	0.94 ± 0.17
H-C	31–40	21	18.8 ± 1.2	457 ± 37	89 ± 2	174 ± 8	10 ± 1	49 ± 5	187 ± 17	104 ± 8	0.73 ± 0.12
H-D	41–50	28	18.0 ± 0.7	431 ± 23	91 ± 2	175 ± 4	9 ± 1	46 ± 5	193 ± 20	103 ± 12	0.94 ± 0.13
H-E	≥51	32	17.1 ± 0.7	379 ± 26	100 ± 2	184 ± 7	10 ± 1	47 ± 3	212 ± 17	115 ± 9	0.69 ± 0.08
Hyperthyroid patients during euthyroid state											
E-A	10–20	16	8.2 ± 1.0	122 ± 31	86 ± 2	125 ± 5	13 ± 1	53 ± 5	87 ± 9	106 ± 11	1.34 ± 0.18
E-B	21–30	16	7.3 ± 0.7	126 ± 10	82 ± 3	125 ± 6	8 ± 1	42 ± 3	87 ± 13	91 ± 9	1.08 ± 0.13
E-C	31–40	21	5.1 ± 0.7	136 ± 11	81 ± 1	126 ± 6	9 ± 1	37 ± 4	113 ± 14	69 ± 8	0.88 ± 0.18
E-D	41–50	28	6.3 ± 0.5	131 ± 8	85 ± 3	127 ± 5	9 ± 1	42 ± 4	93 ± 12	69 ± 6	0.59 ± 0.09
E-E	≥51	32	6.9 ± 0.6	146 ± 13	84 ± 2	129 ± 5	9 ± 1	44 ± 4	84 ± 12	83 ± 6	0.72 ± 0.11
Subjects with alimentary hyperglycemia due to gastrectomy											
G-E	≥51	12	8.4 ± 0.4	126 ± 3	90 ± 2	178 ± 7	8 ± 1	84 ± 21	210 ± 34	183 ± 42	1.01 ± 0.23
Statistical analysis											
C-A vs. C-C						$P < 0.005$					
C-A vs. C-D						$P < 0.005$					
C-A vs. C-E						$P < 0.005$			$P < 0.001$		$P < 0.001$
C-A vs. H-A					$P < 0.005$	$P < 0.001$	$P < 0.001$	$P < 0.005$	$P < 0.005$	$P < 0.001$	
C-B vs. H-B						$P < 0.001$					
C-C vs. H-C						$P < 0.001$					
C-D vs. H-D						$P < 0.001$					
C-E vs. H-E					$P < 0.001$	$P < 0.001$		$P < 0.005$	$P < 0.005$		
H-A vs. H-C								$P < 0.001$		$P < 0.001$	$P < 0.005$
H-A vs. H-D								$P < 0.001$		$P < 0.001$	$P < 0.005$
H-A vs. H-E					$P < 0.05$	$P < 0.05$	$P < 0.01$	$P < 0.001$	$P < 0.05$	$P < 0.001$	$P < 0.001$
E-A vs. E-D										$P < 0.005$	
E-A vs. E-E											$P < 0.005$
E-B vs. E-E											$P < 0.005$
H-E vs. G-E					$P < 0.005$			$P < 0.005$		$P < 0.01$	$P < 0.05$
H-D vs. E-D						$P < 0.001$			$P < 0.001$	$P < 0.005$	
H-E vs. E-E					$P < 0.001$	$P < 0.001$			$P < 0.001$	$P < 0.001$	
H-A vs. E-A						$P < 0.001$		$P < 0.001$	$P < 0.001$	$P < 0.001$	
H-B vs. E-B						$P < 0.001$		$P < 0.005$	$P < 0.005$	$P < 0.005$	
H-C vs. E-C					$P < 0.005$	$P < 0.001$		$P < 0.005$	$P < 0.005$	$P < 0.005$	

*Mean ± SE.

zole therapy and had been in euthyroid state for 2 wk as judged by normal serum T_4 and T_3 concentrations (Table 1). They were divided according to age into five groups: E-A group, 10–20 yr; E-B group, 21–30 yr; E-C group, 31–40 yr; E-D group, 41–50 yr; and E-E group; ≥51 yr.

Fasting BG was not significantly different between the five groups in euthyroid state (Table 1 and Figure 1). When compared with that of pretreatment, fasting BG reduced, more or less, in all groups after treatment but the difference was significant only in C and E groups (Table 1 and Figure 1). After glucose administration, the peak BG and ΣBG also decreased significantly in all groups (Figure 1 and Table 1) in euthyroid state, and the peak was at 30 min not only in young patients but also in patients ≥51 yr (Figure 1 and Table 1).

After glucose administration, serum IRI increased, and the peak value was found 30 min after glucose administration in all groups (Figure 2 and Table 1). Except D and E groups, the peak value was significantly less during euthyroid state than during hyperthyroid state. After treatment, the IRI area above fasting level (ΣIRI) decreased significantly in all groups (Table 1). Since the decrease of ΣBG slightly exceeded the

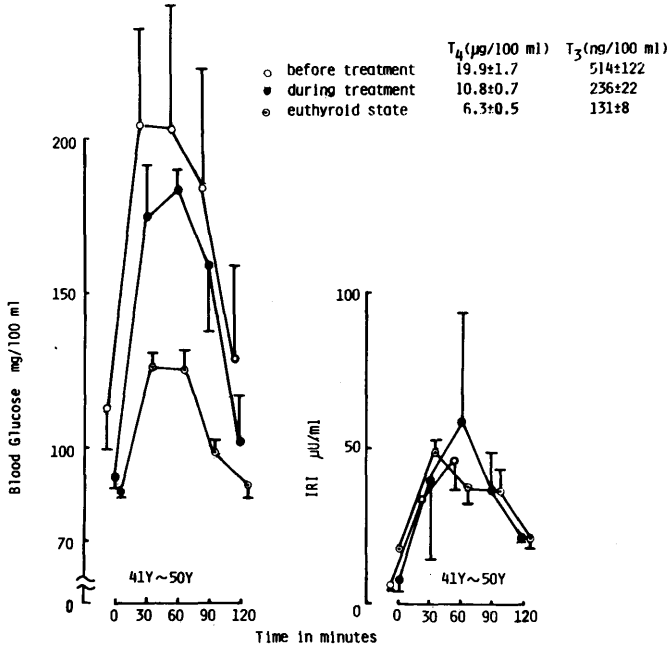

FIG. 3. Blood glucose and insulin concentrations before (overtly hyperthyroid) and during (moderately hyperthyroid and euthyroid) antithyroid drug therapy in middle-aged (41–50 yr) hyperthyroid patients. Oral glucose (50 g) was administered at 0 time. Circles and horizontal lines indicate mean ± SE.

decrease of ΣIRI, the ΣIRI/ΣBG ratio increased slightly in the B, C, and E groups after treatment (Table 1). Except for the E-D group, the pattern of age-related depression of the ΣIRI/ΣBG ratio was again found, but the difference was not statistically significant.

Blood glucose and serum insulin in overtly hyperthyroid, moderately hyperthyroid, and euthyroid states. In six middle-aged (41–50 yr) hyperthyroid patients (not included in Figures 1 and 2 or in Table 1), OGTT was performed repeatedly in overtly hyperthyroid (before treatment), moderately hyperthyroid (early phase of treatment), and euthyroid (about 3 mo after initiation of treatment) states.

As shown in Figure 3, glucose tolerance gradually improved as serum T_4 and T_3 decreased. As compared with euthyroid state, glucose intolerance was still found under moderately hyperthyroid state. No significant change was found in serum IRI in this group of patients under hyperthyroid, moderately hyperthyroid, and euthyroid states.

Blood glucose and serum insulin in normal subjects of different ages. One hundred twelve normal subjects were similarly divided according to age: C-A group, 10–20 yr; C-B group, 21–30 yr; C-C group, 31–40 yr; C-D group, 41–50 yr; and C-E group, ≥51 yr.

Except for the C-C group, the peak value of BG and ΣBG after 50-g OGTT increased progressively with age (Table 1). The peak was at 30 min in all groups (Figure 4). On the other hand, the peak IRI, which appeared at 30–60 min, and ΣIRI did not change with advancing age (Figure 5 and Table

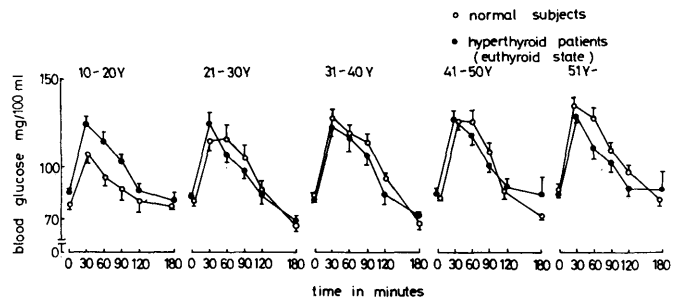

FIG. 4. Age-related changes of glucose tolerance in normal subjects (○) and euthyroid patients with Graves's disease (●). Oral glucose (50 g) was administered at 0 time. Circles and horizontal lines indicate mean ± SE.

1). The ΣIRI/ΣBG ratio decreased progressively with age (Table 1). When treated hyperthyroid patients in euthyroid state were compared with normal subjects, none of the indices of glucose tolerance were significantly different (Table 1).

Blood glucose and serum insulin in patients with hyperglycemia due to gastrectomy. Fifty-gram OGTT was performed in 12 old (≥51 yr) patients with early-phase hyperglycemia of >5 yr duration due to gastrectomy. The peak BG level in gastrectomized patients (Table 1) was similar to that in age-matched untreated hyperthyroid patients (Table 1), although the peak appeared earlier in gastrectomized patients (Figure 6, left panel). The ΣBG was the same in both groups. However, there was a marked difference in IRI concentration between the two groups (Figure 6, right panel). The peak IRI and ΣIRI were considerably higher in patients with gastrectomy than in patients with untreated hyperthyroid. Thus, hyperthyroidism blunted the expected increase of serum insulin concentration. As a result, the ΣIRI/ΣBG ratio was significantly higher in the former (Table 1).

Insulin radioreceptor assay for erythrocytes from normal subjects or from hyperthyroid patients. The maximal binding of ^{125}I-labeled insulin to the erythrocytes was less in old normal subjects than in young normal subjects (Figure 7, A and B; Table 2). The maximal binding was less in young and old hyperthyroid patients than in age-matched controls (Figure 7, C and D; Table 2). However, the value in young and old patients was comparable with that of age-matched controls

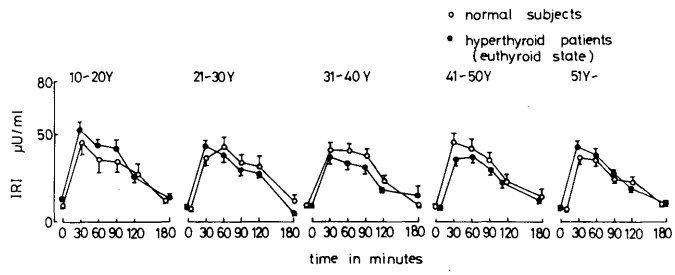

FIG. 5. Insulin secretion in response to 50 g glucose in normal subjects (○) of different ages and in euthyroid patients (●) with Graves's disease. Circles and horizontal lines indicate mean ± SE.

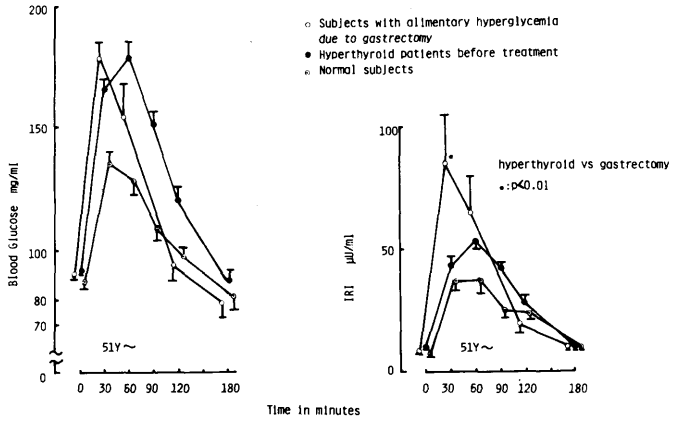

FIG. 6. Blood glucose and insulin concentrations in patients with early-phase hyperglycemia due to gastrectomy (○), in untreated patients with Graves's disease (●) and in normal subjects (○). Circles and horizontal lines indicate mean ± SE.

when euthyroidism was produced by appropriate treatment (Figure 7, E and F; Table 2). Reticulocyte counts were within normal range (0.5–1.2%) in all groups and were not significantly different among the groups.

When the data were subjected to Scatchard analysis, curvilinear plots were obtained (Figure 7, A–F) in normal subjects and hyperthyroid patients. The number of insulin receptors was significantly less in old than in young normal subjects (Figure 7, A and B; Table 2); however, aging did not affect the insulin binding affinity to erythrocytes (Table 2).

In untreated hyperthyroid patients, the number of insulin receptors of erythrocytes was significantly decreased compared with age-matched normal subjects (Figure 7, C and D; Table 2). The binding affinity was not affected by either age or hyperthyroid state. When serum thyroid hormone concentrations were normalized by antithyroid drug therapy, the number of insulin receptors of erythrocytes returned to normal in hyperthyroid patients (Figure 7, E and F; Table 2).

DISCUSSION

In agreement with a number of previous reports,[7,12–17] our present study indicates that disposal of a glucose load is progressively impaired in normal subjects during aging, although insulin secretion is not significantly impaired in peak value attained and the area above fasting level. As a result, ΣIRI/ΣBG ratio decreases progressively with age in normal subjects. Our present study of 113 patients with Graves's disease clearly indicates that the changes of BG levels with advancing age are relatively more in overtly hyperthyroid patients. Such an age-related glucose intolerance is less marked when serum T_3 and T_4 concentrations of the six patients are reduced to levels moderately above normal. Since glucose intolerance is completely normalized when euthyroidism is established by treatment, an increase of circulating thyroid hormone is largely responsible for the observed changes.

Our first attempt was to study insulin response in patients with Graves's disease before and during treatment. In accordance with our previous study,[7] hyperthyroidism did not reduce the expected increase of insulin secretion in response to glucose load in young patients. In contrast, hyperthyroidism blunted the expected increase of insulin secretion in old patients. In support of this concept, insulin response was indistinguishable from that of age-matched controls when euthyroidism was established by appropriate treatment. Thus, age-related, decreased insulin secretion in old patients is in fact one of the factors responsible for age-related glucose intolerance in patients with Graves's disease.

Although contradictory results have been reported,[18–20] an alternative hypothesis would be that pancreatic insulin reserve decreased progressively with age and, under such a con-

TABLE 2
Binding of insulin with RBC

Group	Age* (yr)	No. of subjects	Total binding (%)	Affinity constant (10^8 M^{-1})	Binding capacity (10^{-10} M)	Sites/cell
Normal young	23 ± 1	10	4.84 ± 0.24	2.03 ± 0.24	2.57 ± 0.28	52 ± 6
Normal old	57 ± 3	11	3.45 ± 0.12	2.32 ± 0.34	1.91 ± 0.18	35 ± 4
Hyperthyroid young	23 ± 2	10	3.75 ± 0.19	2.22 ± 0.33	1.64 ± 0.13	30 ± 2
Hyperthyroid old	54 ± 2	11	2.75 ± 0.18	2.21 ± 0.46	1.37 ± 0.24	27 ± 5
Treated hyperthyroid young	25 ± 3	10	4.71 ± 0.32	2.16 ± 0.19	2.35 ± 0.27	45 ± 7
Treated hyperthyroid old	51 ± 2	10	3.77 ± 0.21	2.27 ± 0.39	1.95 ± 0.29	37 ± 5
Statistical analysis						
A vs. B			$P < 0.001$		$P < 0.05$	$P < 0.05$
A vs. C			$P < 0.01$		$P < 0.02$	$P < 0.05$
B vs. D			$P < 0.01$		$P < 0.05$	
C vs. E			$P < 0.02$		$P < 0.05$	$P < 0.05$
D vs. F			$P < 0.001$		$P < 0.05$	

*Mean ± SE.

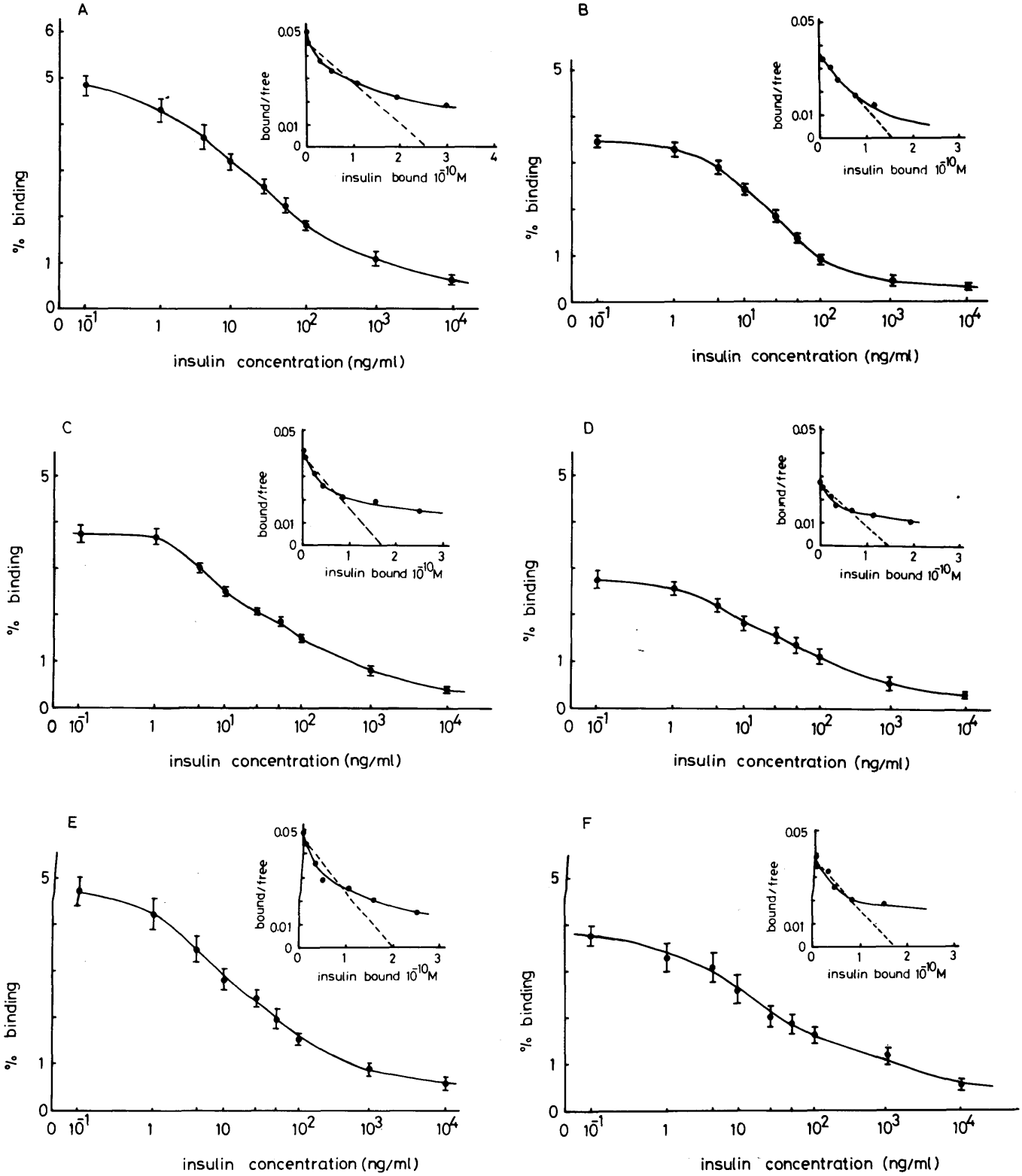

FIG. 7. Insulin receptors of the red blood cells in young normal subjects (A), old normal subjects (B), young untreated hyperthyroid patients (C), old untreated hyperthyroid patients (D), young treated hyperthyroid patients (E), and old treated hyperthyroid patients (F). Displacement curve and Scatchard plots are shown. Circles and horizontal lines indicate mean ± SE calculated in 10–11 subjects.

dition, prolonged hyperglycemia, whatever its exact cause, may produce age-related decrease of insulin secretion. However, such an assumption was not confirmed in subjects with gastrectomy who showed early-phase hyperglycemia. This finding raised a possibility that prolonged elevation of serum T_4 and T_3 specifically depresses insulin secretion. In support of this concept, experimental study on rats indicated that T_3 and T_4 treatment inhibited glucose-induced insulin secretion from isolated rat pancreas,[21] but that optimal isomer D-T_4 was without effect in this respect.[22] Since circulating active hormone T_3 did not increase with age, but even decreased slightly in untreated hyperthyroid patients, one may assume that an unknown factor is partially responsible. An alternative hypothesis would be that the pancreas itself is more susceptible to high levels of T_3 as people age and therefore the actual level of T_3, which is a little bit lower in the older patients, is not the critical factor.

Since reduction of hormone receptor concentrations constitutes a fairly common manifestation of the aging process,[23] a possible factor for age-related glucose intolerance would be an alteration of insulin receptor in the cells. Gambhir et al. reported that insulin receptors on human erythrocytes appear to exhibit binding characteristics analogous to those seen in other tissues and shows a similar adaptation in a number of pathologic and experimental conditions.[10,24] Thus, we studied insulin receptors in normal subjects and patients with Graves's disease to determine whether there is age-related alteration in the insulin receptor. In agreement with the report by Kappy and Lotnick,[25] we found a slight but significant decrease of insulin binding capacity in the erythrocytes in old normal subjects. Such an age-related decrease of insulin receptor was also found in human adipose tissue.[26] However, since the decrease is too small, and since Hendricks et al. failed to find such a decrease,[27] it may be safe not to make a definite conclusion. However, we found a definite decrease of binding capacity in old untreated patients when compared with young and old controls. Futhermore, insulin binding capacity, number of receptor, and $\Sigma IRI/\Sigma BG$ ratio normalized in old patients with Graves's disease after appropriate treatment with antithyroid drug. Eng et al.[28] have pointed out that insulin uptake was more in young RBC than in old. However, our present findings do not reflect the difference in the age of erythrocytes as evidenced by the same proportion of reticulocytes among the six groups. Furthermore, under hyperthyroid state, subtle changes in the age of erythrocytes may produce an increase rather than a decrease of insulin binding, since a shorter half-life of erythrocytes can be expected under hypermetabolic and hypercatabolic states. However, this is not the case. Since the initiation of insulin action appears to depend on the interaction of insulin with specific insulin receptor on the plasma membrane,[29] the present findings explain, at least in part, why age-related decrease of $\Sigma IRI/\Sigma BG$ ratio appeared in untreated patients and normalized in treated patients. However, some reservations must be made in interpretating our data since Dons et al.[30] stated that conclusions drawn from RBC measurements may vary from those drawn from measurements made on other tissues.

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