Low Triiodothyronine and Raised Reverse Triiodothyronine Levels in Patients Over Fifty Years of Age Who Have Type II Diabetes Mellitus:

Influence of Metabolic Control, Not Age

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Several studies have demonstrated that the uncontrolled diabetic state in both type I as well as type II diabetes mellitus is characterized by altered thyroid hormone metabolism, which results in the lowering of serum triiodothyronine (T_3) levels and a reciprocal elevation of T_3 (rT_3) levels. Because the majority of type II diabetics are over 50 years of age and because numerous previous reports have implicated aging as a cause of low T_3 and high rT_3 levels, we studied 220 type II diabetics from 40–85 years of age to assess the influence of aging and metabolic control on thyroid hormone levels. Serum thyroxine (T_4) free T_4, T_3 resin uptake, and thyroid-stimulating hormone (TSH) measurements in diabetic patients were not significantly altered compared with 37 young normal control subjects, irrespective of age or the grade of metabolic control. Serum T_3 levels declined and rT_3 levels rose in the diabetic patients with worsening of the metabolic control. However, with comparable metabolic control, the levels were not significantly different from the younger patients. Therefore, low T_3 and high rT_3 levels observed in patients of any age who have type II diabetes mellitus may be exclusively caused by deranged metabolic control of their disease.

The major metabolic pathway of thyroxine (T_4) in humans has been shown to be monodeiodination, which gives rise to either 3,5,3′-triiodothyronine (T_3) or 3,3′,5′-triiodothyronine (rT_3).[1–4] In several disease states, T_4 metabolism is altered, leading to the lowering of serum T_3 and the reciprocal elevation of serum rT_3 concentrations.[3,5–13] This condition is often termed "low T_3 syndrome" or "euthyroid sick disease."

Recently we have reported lower T_3 and raised rT_3 concentrations in patients who had uncontrolled diabetes mellitus.[14,15] Furthermore, normalization of serum T_3 and rT_3 levels was observed with improvement in the metabolic control of their disease as assessed by fasting plasma glucose, glycosylated hemoglobin (HbA1C), and glycosylated protein concentrations.[15,16] Several of these patients had type II or noninsulin-dependent diabetes mellitus (NIDDM). It is well recognized that most type II diabetic patients are over 50 years of age. Several previous studies have suggested that old age alters thyroid hormone metabolism and have found low serum T_3 and high serum rT_3 levels in elderly normal subjects.[17–20] Therefore, to distinguish the influence of aging from that of diabetic control on thyroid hormone metabolism, we examined thyroid hormone concentrations of 170 patients from 50–85 years of age who had type II diabetes mellitus and compared them with the levels of 50 younger type II diabetic patients (under 50 years of age) as well as 37 younger normal subjects (under 50 years of age).

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MATERIALS AND METHODS

Two hundred twenty men (mean age, 68 years, with a range of 40–85 years) who had type II diabetes mellitus and were attending the diabetes clinic at the Veterans Administration Medical Center, Des Moines, Iowa were studied. Informed consent was obtained from each participant. All patients were ambulant at the time of the study, which was performed during a routine follow-up visit to the Clinic. None of the patients manifested ketosis or renal or endocrine dysfunction other than diabetes mellitus as assessed by physical examination, and all had a normal liver profile, BUN and creatinine levels, urinalysis, and other standard

TABLE 1
Glycosylated Hemoglobin (HbA1C) Concentrations in 37 Young Normal Subjects (N) and 220 Type II Diabetes Mellitus (DM) Patients Grouped According to Ages and Grades of Metabolic Control as Defined by Fasting Plasma Glucose (FBS) Concentrations

	FBS (mg/dl)	HbA1C (%)			
		<50 Years	51–60 Years	61–70 Years	>70 Years
N	70–110	6.1 ± 1.3	—	—	—
DM grade I	<140	8.1 ± 0.5 (11)*	8.3 ± 0.4 (17)	7.8 ± 0.5 (15)	7.8 ± 0.9 (8)
DM grade II	141–200	9.7 ± 0.5 (13)†	10.3 ± 0.4 (22)†	10.0 ± 0.5 (15)†	9.7 ± 0.8 (8)†
DM grade III	201–300	11.4 ± 1.3 (16)†	12.3 ± 0.2 (22)†	12.2 ± 0.7 (15)†	12.3 ± 0.4 (8)†
DM grade IV	>300	13.2 ± 1.5 (10)†	14.4 ± 1.4 (19)†	13.6 ± 0.6 (12)†	13.5 ± 0.6 (9)†

* Number of patients in each group is shown in parentheses.
* Significantly higher as compared with N and DM grade I patients ($P < 0.005$).

blood chemistries such as calcium, phosphate, etc. The diabetic patients included 22 newly discovered diabetics, and the duration of the disease in the remaining patients ranged from six months to 15 years. Among the previously known diabetics, 25 were being treated with diet alone, 143 with diet and sulfonylurea, either chlorpropamide or tolazamide, and the remainder with diet and insulin at the time of study. In insulin-treated patients, the diagnosis of type II diabetes mellitus was established by the history of a lack of ketosis and the successful initial management of their diabetes with diet alone or diet plus an oral hypoglycemic agent with subsequent secondary failure of these drugs to provide adequate metabolic control, necessitating insulin administration. All new diabetics were treated with diet and chlorpropamide or tolazamide. Diabetics who had concomitant disorders such as hypertension or atherosclerotic heart disease, as well as those being treated with other medications, were excluded. Thirty-seven young normal subjects (mean age, 38 years, with a range of 22–49 years) judged not to be diabetics by the criteria established by National Diabetes Data Group were also studied.[21]

Twenty-milliliter blood samples were obtained from an antecubital vein after an overnight fast. A 5-ml aliquot was used for determination of the plasma glucose concentration using a Technicon Autoanalyzer® (Technicon Instrument Co., San Francisco, Cal.). A 3-ml sample of blood was used for estimation of the glycosylated hemoglobin (HbA1C) concentration using a Glycogel® test kit (Pierce Chemical Company, Rockford, Ill.). The remaining portion was collected in a cooled tube and centrifuged at 4°C. Serum was extracted and frozen at −20°C for determination of T_4, T_3, rT_3, free T_4, and TSH concentrations at a later date by the methods previously described.[22–26] Determination of T_3 resin uptake was made using a commercial kit with talc and inert fillers as adsorbents (Thyrostat-3,® E. R. Squibb and Sons, Princeton, N.J.). The statistical analyses of the data were performed by student's *t* test and correlation coefficients.

RESULTS

The patients were divided into four groups according to age (Table 1). These groups were further subdivided depending on the degree of metabolic control of their diabetes. The metabolic control was graded according to fasting plasma glucose concentrations, grade 1 being the most adequate control and grade IV denoting the other extreme (Table 1). Patients with fasting plasma glucose concentrations below 140 mg/dl were considered to have well-controlled diabetes (grade I), as this level is one of the criteria established by the National Diabetes Data Group for the diagnosis of diabetes mellitus.[21] The rest of the grading was performed arbitrarily as described in our previous study.[15] Serum HbA1C concentrations corresponded very closely with fasting plasma glucose concentrations in these diabetic patients and further confirmed the grades of metabolic control (Table 1).

Serum T_4, free T_4, T_3 resin uptake, and TSH values were not significantly different in diabetic patients >50 years of age compared with younger diabetic patients and younger control subjects (Table 2). Furthermore, the grade of metabolic control did not influence these concentrations. Serum T_3 declined and serum rT_3 rose with worsening of

TABLE 2
Serum T_4, Free T_4, T_3 Resin Uptake (T_3RU), and Thyroid Stimulating Hormone (TSH) Concentrations in 37 Normal Subjects (N), 50 Type II Diabetes Mellitus Patients <50 Years of Age, and 170 Type II Diabetes Mellitus Patients >50 Years of Age

	T_4 (μg/dl)	Free T_4 (ng/dl)	T_3RU (%)	TSH (μIU/ml)
N	8.1 ± 0.5 (5.0–11.4)	1.9 ± 0.1 (1.2–2.9)	39 ± 2 (35–44)	4.4 ± 0.6 (1.9–7.0)
DM <50 yr	8.7 ± 0.4 (4.8–11.2)	2.2 ± 0.2 (1.3–3.1)	38 ± 2 (34–46)	3.6 ± 0.7 (1.7–7.2)
DM >50 yr	7.9 ± 0.6* (4.9–10.9)	1.9 ± 0.2* (1.2–3.1)	37 ± 3* (33–42)	4.1 ± 0.5* (1.7–6.9)

* Values were not significantly different when type II diabetes mellitus patients were grouped according to age and grade of metabolic control as shown in Table 1.

the metabolic control as documented by rising fasting plasma glucose and serum HbA1C concentrations (Tables 3, 4). However, we failed to find a relationship between these abnormal thyroid hormone levels and the ages of patients (Tables 3, 4). Furthermore, in diabetic patients, there were significant positive correlations between rT_3 and fasting plasma glucose ($r = 0.528$, $P < 0.001$) and serum HbA1C levels ($r = 0.613$, $P < 0.001$). Simultaneously, significant inverse relationships were observed between serum T_3 and plasma glucose ($r = -0.511$, $P < 0.001$) or serum HbA1C ($r = -0.578$, $P < 0.001$) concentrations. Body weight, the duration of the diabetes, and the nature of the treatment failed to demonstrate correlations with thyroid hormone levels, nor did the duration of symptoms do so in patients who had newly discovered diabetes. The T_3/T_4 ratios were decreased in uncontolled diabetic groups (Table 5); moreover, the rT_3/T_4 ratios were simultaneously raised in these same groups (Table 6). Ages of the patients appeared to have no effect on T_3/T_4 or rT_3/T_4 ratios when patients with equivalent levels of metabolic control were compared, as documented by fasting plasma glucose and serum HbA1C levels (Tables 5, 6).

DISCUSSION

These studies demonstrate that T_3 and rT_3 may be the only thyroid hormones altered in the uncontrolled diabetic state. Serum T_4, free T_4, T_3 resin uptake, and TSH values were not significantly different in diabetic patients of all ages, and were unaffected by the grade of metabolic control, when compared with young control subjects. Similar findings were documented in our previous studies[14-16] as well as in several other reports.[27-30] In diabetic patients, serum T_3 declined and rT_3 levels rose as the degree of metabolic control worsened, as reflected by rising fasting plasma glucose and serum HbA1C concentrations. However, serum T_3 and rT_3 levels were not significantly different in diabetics over 50 years of age from those observed in younger patients when the degree of metabolic control was comparable (Tables 3, 4). Thus, aging does not seem to contribute to altered T_3 and rT_3 levels in type II diabetics. This finding may be consistent with the previous report[31] that old age may not cause alterations in serum T_3 and rT_3 levels unless accompanied by an acute or a chronic debilitating disorder. Our patients were a group of nonhospitalized, apparently healthy, ambulant diabetics without an associated acute or chronic illness who did not manifest abnormal hepatic or renal function at the time of study. Thus, none of the factors known to induce alterations in thyroid hormone metabolism were present in our patients.[3,8,9-12,32] The changes in serum T_3 and rT_3 concentrations may therefore be attributed to the decompensated diabetic state alone—a finding that is consistent with our recent studies on diabetic populations with both types I and II diabetes mellitus.[14-16]

This study suggests that the lowering of serum T_3 concentrations in uncontrolled diabetic patients may be secondary to impaired T_3 synthesis from T_4 monodeiodination as demonstrated by the decreased T_3/T_4 ratios of patients with deranged metabolic control (Table 5). (However, enhanced metabolic clearance and/or degradation of T_3 may be responsible as well.) The rise in serum rT_3 in the same diabetic population may be secondary to decreased turnover and/or clearance of circulating rT_3, as suggested in a previous study of a population of type I diabetes mellitus patients.[28] Alternately, increased rT_3 synthesis from T_4 as reflected by an elevated rT_3/T_4 ratio (Table 6) may have contributed to the raised serum rT_3 concentrations found in this study.

Thus, the alterations in serum T_3 and rT_3 levels observed in elderly type II diabetes mellitus patients may be induced by inadequate metabolic control alone.

TABLE 3
*Serum Triiodothyronine Concentrations in 37 Young Normal Subjects (N) and 220 Type II Diabetes Mellitus (DM) Patients**

	T_3 (ng/dl)			
	<50 Years	51–60 Years	61–70 Years	>70 Years
N	135 ± 5	—	—	—
DM grade I	133 ± 5	133 ± 5	129 ± 5	136 ± 9
DM grade II	116 ± 7†	120 ± 4†	113 ± 5†	121 ± 7†
DM grade III	109 ± 6†	107 ± 6†	109 ± 8†	106 ± 8†
DM grade IV	97 ± 4†	96 ± 7†	98 ± 4†	97 ± 6†

* DM patients are grouped according to age and grade of metabolic control as shown in Table 1.

† Significantly lower compared with N and DM grade I patients $P < 0.01$.

TABLE 4
*Serum Reverse Triiodothyronine (rT_3) Concentrations in 37 Young Normal Subjects and 220 Type II Diabetes Mellitus (DM) Patients**

	rT_3 (ng/dl)			
	<50 Years	51–60 Years	61–70 Years	>70 Years
N	12 ± 2	—	—	—
DM Grade I	12 ± 2	14 ± 4	13 ± 2	14 ± 2
DM Grade II	24 ± 3†	22 ± 2†	21 ± 3†	23 ± 5†
DM Grade III	27 ± 3†	23 ± 2†	24 ± 3†	28 ± 5†
DM Grade IV	36 ± 5†	33 ± 4†	34 ± 4†	32 ± 4†

* DM patients are grouped according to age and grade of metabolic control as shown in Table 1.

† Significantly higher compared with N and DM grade I patients ($P < 0.005$).

TABLE 5
*Triiodothyronine/Thyroxine (T_3/T_4) Ratios in 37 Young Normal Subjects (N) and 220 Type II Diabetes Mellitus (DM) Patients**

	T_3/T_4 Ratios†			
	<50 Years	51–60 Years	61–70 Years	>70 Years
N	17.2 ± 0.2	—	—	—
DM Grade I	16.8 ± 0.2	16.7 ± 0.3	16.6 ± 0.4	17.2 ± 0.3
DM Grade II	13.1 ± 0.5‡	15.1 ± 0.3‡	15.2 ± 0.3‡	15.5 ± 0.2‡
DM Grade III	13.3 ± 0.2‡	13.5 ± 0.6‡	12.9 ± 0.4‡	12.9 ± 0.7‡
DM Grade IV	11.2 ± 0.6‡	12.1 ± 0.4‡	11.4 ± 0.4‡	12.4 ± 0.5‡

* DM patients are grouped according to age and grade of metabolic control as shown in Table 1.
† T_3 concentrations are reported in nanograms and T_4 concentrations, in micrograms.
‡ Significantly different from N and DM grade I patients ($P < 0.05$).

TABLE 6
*Reverse Triiodothyronine/Thyroxine (rT_3/T_4) Ratios of 37 Young Normal Subjects (N) and 220 Type II Diabetes Mellitus (DM) Patients**

	rT_3/T_4 Ratios†			
	<50 Years	51–60 Years	61–70 Years	71–80 Years
N	1.48 ± 0.11	—	—	—
DM grade I	1.46 ± 0.13	1.68 ± 0.14	1.70 ± 0.12	1.82 ± 0.13
DM grade II	2.72 ± 0.19‡	2.82 ± 0.13‡	2.84 ± 0.13‡	2.66 ± 0.15‡
DM grade III	3.13 ± 0.38‡	2.91 ± 0.17‡	2.85 ± 0.26‡	3.38 ± 0.37‡
DM grade IV	4.00 ± 0.21‡	4.18 ± 0.27‡	3.95 ± 0.36‡	4.12 ± 0.55‡

* DM patients are grouped according to age and grade of metabolic control as shown in Table 1.
† rT_3 concentrations are reported in nanograms and T_4 concentrations, in micrograms.
‡ Significantly different from N and DM grade I patients ($P < 0.001$).

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The American Geriatrics Society
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In compliance with Article VIII, Section 1, of the By-Laws, the Nominating Committee of The American Geriatrics Society will present the following unanimously agreed upon slate of Officers and Directors for approval by Members of the 1984 Annual Business Meeting to be held at the Denver Hilton Hotel, Denver, Colorado, at 5:15 PM on Thursday, May 17, 1984.

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