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THE EFFECTS OF DIABETES MELLITUS ON THYROID PHYSIOLOGY



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Thyroid hormone enhances the absorption, production and utilization of glucose. Often, latent diabetes may become unmasked by hyperthyroidism while hypoglycemia is sometimes a manifestation of hypothyroidism. However, until recently the presence and possible clinical impact of abnormal thyroid function in insulin-dependent diabetic patients have received very little attention. Diabetes mellitus appears to influence thyroid function at several sites, from hypothalamic control of thyroid-stimulating hormone (TSH) release to 3,5,3'-triiodothyronine (T3) production from thyroxine (T4) in the target tissue. The best studied effect is the lowered circulating T3 in diabetic patients. The following review summarizes the current state of the art concerning the effects of diabetes mellitus on the peripheral metabolism of thyroid hormone. The regulation of thyroid hormone metabolism will be described only briefly since the subject was reviewed by Cavalieri in a recent issue of *Thyroid Today* (Vol. 3, No. 7).

Normal Thyroid Hormone Metabolism

The past decade has seen significant gains in our understanding of the production and metabolism of thyroid hormone in both health and disease. Data from several studies indicate that the thyroid of a normal adult in steady state secretes approximately 100 nanomoles of T4, 8 nanomoles of T3, and 2 nanomoles or less of 3,3',5'-triiodothyronine (rT3) each day.¹⁻³ In terms of total production rate, this represents about 100% of T4, but only 20% of T3, and 5% of rT3, although the thyroidal secretion of T3 may increase by two- or threefold from a stimulated thyroid. Following thyroidal release, all the iodothyronines undergo sequential monodeiodination in nearly every peripheral tissue including the thyroid itself (Figure 1). The formation of T3 represents a three- to fivefold

gain in activity over that of T4 per se, whereas rT3 is nearly inert when compared to the substrate, T4. In steady state, approximately 32% of T4 produced is deiodinated at the 5' position on the phenolic ring to form T3; 45% of T4 produced is deiodinated at the 5 position on the alanyl ring. T4 deiodination is the major source of circulating T3 and rT3.

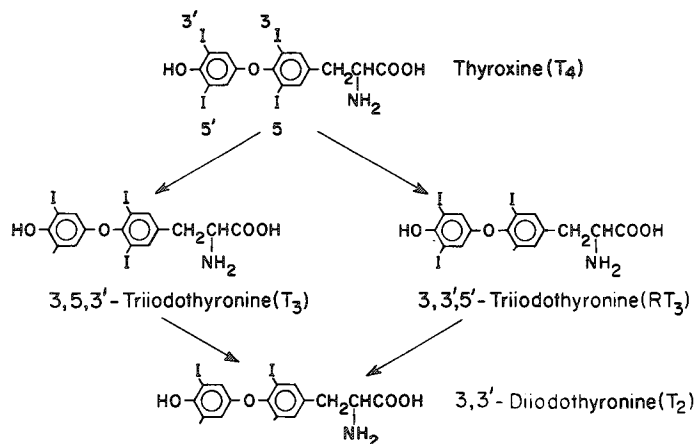


Figure 1.
Thyroxine metabolism by deiodination.

Only a few of the details of the T3 deiodination within the target tissue are understood. The deiodination reactions at 5 and 5' may be dissociated in clinical disorders and in experimental conditions. Therefore, there appear to be at least two enzymes, a 5-deiodinase and a 5'-deiodinase. These reactions may be enhanced *in vitro* by enriching the tissue content of reduced glutathione. Both cell membrane and microsome have high deiodinase activity. Indirect evidence suggests that these same enzymes also modulate the sequential monodeiodination of T3, rT3, and other partially iodinated thyronines. The T3 produced *in situ* is bound to specific nuclear T3 receptors and leads to enhanced transcription rates and protein synthesis. Therefore, the appropriate T4 deiodination and T3-receptor complex formation are central to the manifestation of the biological effects of thyroid hormone such as growth, maturation, and energy metabolism.

The Low-T3 Syndrome in Acute and Chronic Illnesses

Deiodination of iodothyronines is inhibited by a host of

pathological factors and drugs, and above all else by alteration of glucose metabolism. Fasting or a low carbohydrate diet leads to reduced T3 production while overfeeding results in elevated T3 production.⁴⁻⁶ Hepatic cirrhosis, renal failure, surgical procedure and other acute and chronic illnesses may give low circulating T3 values.^{7,8} A number of drugs such as ipodate (Oragrafin®), iopanoic acid (Telepaque®), dexamethasone, propranolol and propylthiouracil which are commonly used for the diagnosis or treatment of these conditions also reduce the conversion of T4 to T3.⁹⁻¹²

Nearly all of the pathological conditions that have been studied in detail reduce the production of T3 from T4 and slow the metabolic clearance of rT3 by inhibiting deiodination primarily at the 5' position of these iodothyronines. Since the fractional T4 disposal undergoing deiodination remains unchanged, there appears to be shunting of T4 away from the production of T3 and into the production of more rT3. Studies of normal adults show that approximately 77% of T4 disposal undergoes monodeiodination at either the 5 or 5' position, while 78% of T3 disposal in fasting normal subjects and 76% of T4 disposal in patients with hepatic disorders undergo monodeiodination.^{4,7} Typically these patients present divergent changes of thyroid function tests showing normal T4, reduced T3, and elevated rT3 values in blood. This is commonly known as the low-T3 syndrome. The clinical manifestation of myxedema is usually absent in these patients and their serum TSH levels commonly remain within normal limits.

Thyroid Function in Diabetes Mellitus

Thyroid hormone metabolism is altered in diabetes mellitus as well as in many other acute and chronic illnesses. The low-T3 syndrome is always present in patients in diabetic ketoacidosis. However, because the general diabetic population is heterogeneous, the clinical manifestations of such altered thyroid function may be varied. Also the disorder of their thyroid hormone metabolism is both more prolonged and more severe than the changes seen in the normal subjects undergoing fasting.

In general, the severity of the disturbance of thyroid hormone metabolism reflects the severity of insulin deficiency and disturbance of glucose metabolism. In patients with exogenous obesity and mild glucose intolerance, circulating T3 values often remain within normal limits or are even slightly elevated since overfeeding enhances the conversion of T4 to T3.⁶ A cursory examination of the mean values from small groups of diabetic patients usually fails to reveal any significant abnormality in thyroid function, but studies of larger patient groups reveal impaired T3 production even in the treated and stable clinic population (Figure 2).^{13,14} Recently, our laboratory evaluated the serum T3:T4 ratio in diabetes which may be taken as a parameter of T3 production from T4. Results from 33 normal controls and 50 diabetic clinic patients showed a lower mean T3:T4 ratio in the diabetic group. Furthermore, both the serum T3 level and the T3:T4 ratio showed an inverse correlation with both the fasting blood glucose level and the glycosylated hemoglobin value (Figure 2). Saunders, Hall, and Sönksen studied 11 insulin-dependent diabetic patients and found the serum T3 levels to be positively correlated with the rates of glucose clearance and utilization, and negatively correlated with the concentrations of plasma ketone body.¹⁵ Postellon, Becker, and Foley also reported a significant correlation between serum T3, blood pH, and bicarbonate levels in newly diagnosed patients with juvenile

onset diabetes.¹⁶ Serum rT3 values were widely scattered and failed to show any correlation with serum T3:T4 ratio, pH, or bicarbonate levels.

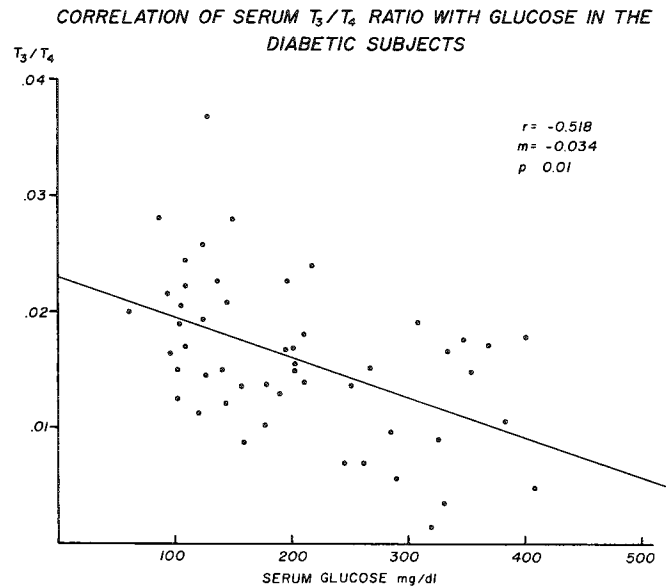


Figure 2. Comparison of serum T3 and fasting glucose levels in the diabetic clinic population.

The Hypothalamic-Pituitary-Thyroid Axis in Diabetes Mellitus

The effects of diabetes on the hypothalamic-pituitary-thyroid axis are not well understood. Experimentally induced diabetes in animals caused a significant reduction in TRH and TSH levels as well as T4 and T3 levels in peripheral blood.¹⁷ In the same animals the TRH binding capacity of the pituitary plasma membrane remained unchanged. Thus, experimental diabetes may result in a reduction in the stimulation of the thyroid as a consequence of a diminution in hypothalamic and pituitary factors. In man, the results are somewhat more complex. The serum T4 concentration in diabetic patients was reported to be elevated, normal, or lowered.^{14,15,18} Studies by Naeije and colleagues of patients in diabetic ketoacidosis and by our laboratory showed a remarkable blunting of pituitary response to TRH stimulation.¹⁹ Therefore, diabetes mellitus and the stress of ketoacidosis have an inhibitory effect on the pituitary itself. Diabetic ketoacidosis is usually associated with elevated blood levels of free fatty acid; a high free fatty acid level increases both the free T4 fraction and free T4 concentration, which also may have an inhibitory influence on pituitary TSH release.²⁰ Further study in this area is needed.

Thyroid Hormone Metabolism in Diabetes Mellitus

Diabetes mellitus has a strong inhibitory effect on the deiodination of T4 as well as the stepwise deiodination of the other partially iodinated thyronines. This effect appears to be more marked on the phenolic ring than the alanyl ring. Turnover studies with radioisotope labeled T4, T3, and rT3 have been carried out in diabetic patients with and without insulin dependence (Table 1).^{13,21} The metabolic clearance

rates of T4 and T3 are within normal range. The metabolic clearance rate of rT3 remains normal in insulin-independent diabetic patients but is significantly reduced in insulin-dependent diabetic patients. The T3 disposal rate on a daily dose of 0.2 mg T4 is lower than normal in both diabetic groups: 36.3 $\mu\text{g/day}$ in the normal controls, 20.3 $\mu\text{g/day}$ in insulin-independent diabetic patients, and 10.6 $\mu\text{g/day}$ in insulin-dependent diabetic patients. The T4 to T3 conversion rate is 35% in normal controls, 15% in the insulin-independent diabetic patients, and 6.8% in insulin-dependent diabetic patients.

The rT3 disposal rate of 54.0 $\mu\text{g/day}$ is slightly increased in insulin-dependent diabetic patients compared to 45.9 $\mu\text{g/day}$ in normal controls. However, these diabetic patients also have a lower T4 to rT3 conversion rate of 33.1% as compared to 41.8% in normal controls. Therefore, in the more severely diabetic individuals, there is very little shunting of T4 away from T3 production into rT3 production. The fractional T4 disposal converted to both T3 and rT3 is significantly lower in diabetic patients whereas it is unchanged in hepatic cirrhosis or starvation (Figure 3).

The more generalized inhibitory effect of diabetes on deiodination has also been demonstrated by *in vitro* studies with liver homogenate prepared from animals with experimental diabetes.²² It can be shown that such liver preparations have a lower capacity to convert T4 into T3 or rT3 and also have a lower capacity to convert T3 and rT3 into diiodothyronines and moniodothyronines.²³ This inhibitory effect may be unrelated to a reduced sulfhydryl concentration in the tissue since the addition of dithiothriitol has little influence on the deiodination reaction and the concentration of non-protein sulfhydryl groups remains normal in the brain, heart, liver, kidney and skeletal muscles.²⁴ It is possible that diabetes mellitus inhibits deiodinase activity directly. Additional studies are required to resolve this issue.

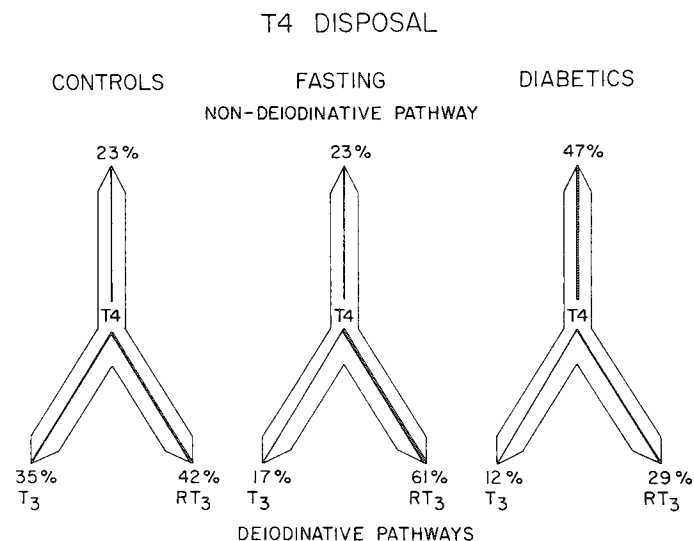


Figure 3.

When insulin therapy is given, thyroid hormone metabolism returns toward normal in diabetic patients but at a very slow rate. A low dose of insulin given as intravenous infusion over ten hours fails to change circulating T3 and rT3 values appreciably. Often, it takes 5 to 14 days of rigorous diabetic control with both diet and insulin to alleviate the low-T3

syndrome.^{19,21} Still, T3 production remains lower than the normal population (Figure 4).

TRIIODOTHYRONINE PRODUCTION IN DIABETIC PATIENTS ON T₄ REPLACEMENT 0.2mg/day

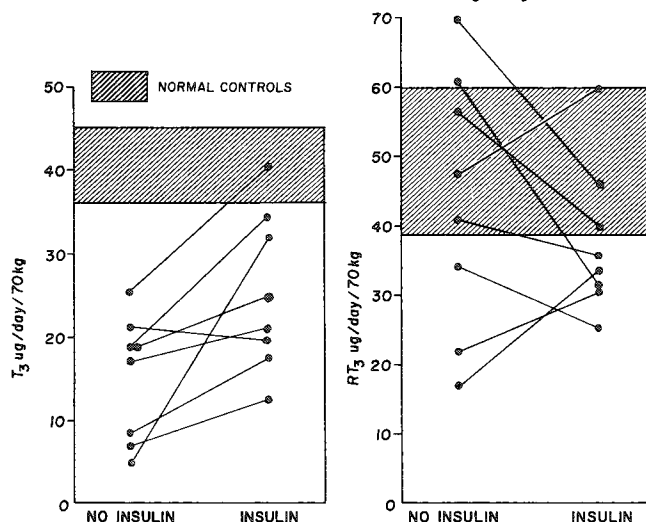


Figure 4.

The Clinical Significance of Chronic Low-T3 Syndrome

It is almost certain that some degree of low-T3 syndrome is present for many decades in poorly controlled insulin-dependent diabetic patients. But its clinical significance is not well understood. The possibility of tissue hypothyroidism in patients with low-T3 syndrome is often rejected on the ground that serum TSH values are usually normal. However, this is probably not a valid argument against hypothyroidism in view of the fact that diabetes also impairs hypothalamic and pituitary functions. The low-T3 syndrome also has been viewed as an advantageous adjustment of conservation. According to this hypothesis, lowering the T3 production may help the host to better withstand catabolism during stress, illness, or starvation.

Curiously, Saunders and colleagues have reported higher than normal oxygen consumption in patients with ketoacidosis and low serum T3 levels.¹⁵ More recently, Mayfield and colleagues reported a diabetic patient with ketoacidosis who had hyperthyroidism and yet had normal serum T4 and T3 values.²⁵ His T4 and T3 became markedly elevated only upon his recovery from ketoacidosis.

SUMMARY

Thyroid physiology may be altered by diabetes mellitus via several mechanisms. Diabetic subjects may have reduced TRH available to the pituitary as well as a blunted pituitary TSH response to TRH. However, the inhibition of iodothyronine deiodination in the periphery that leads to reduced T3 production from T4 appears to be by far the dominant influence of diabetes mellitus. This defect in T3 production is detectable even in the conventionally treated and stable diabetic population. The lower T3 production is generally not associated with clinical myxedema and clinicians can make a correct diagnosis of low-T3 syndrome by the divergent changes of serum T4, T3, and rT3 values. T3 production as

reflected by serum T3:T4 ratio may in fact be used as an indirect parameter of diabetic control. Occasionally, hyperthyroidism may precipitate overt diabetes mellitus while more rarely diabetic ketoacidosis can mask the presence of

hyperthyroidism. Most important of all, poorly controlled diabetic patients may live with lowered T3 production for many decades. The long-term effects of chronic low-T3 syndrome are not known.

Table 1. Thyroid Hormone Kinetics in Diabetic Patients on L-T4 0.2 mg Daily

Subjects*	Conc μg/dl	T4 MCR l/d	DR μg/d	Conc ng/dl	T3 MCR l/d	DR μg/d	Conc ng/dl	rT3 MCR l/d	DR μg/d
Normal Control									
mean	11.3	1.19	133	173	21.4	36.3	46	98.8	45.9
SD	2.2	0.25	29	37	3.8	6.8	8	14.3	8.6
Insulin-independent diabetic									
mean	11.8	1.33	158	79	24.9	20.3	37	98.9	37.0
SD	1.9	0.17	38	29	5.1	9.1	5	30.3	14.4
Insulin-dependent diabetic									
mean	13.6	1.41	188	44	25.4	10.6	74	74.7	54.0
SD	2.1	0.25	26	26	3.6	5.7	18	39.4	29.3

Conc = serum concentration

MCR = metabolic clearance rate

DR = disposal rate

* = 8 patients or subjects in each category

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