Diabetic Nephropathy Accompanied by Iodine-Induced Non-Autoimmune Primary Hypothyroidism: Two Case Reports

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Abstract. We reported 2 diabetic patients with nephrotic syndrome due to advanced diabetic nephropathy complicated by non-autoimmune primary hypothyroidism. Hypothyroidism developed along with the anasarcan status. Histological examinations of the thyroid gland revealed almost normal thyroid follicles without lymphocytic infiltration. The amounts of thyroid hormone lost into the extravascular space such as in urine and ascites were not sufficient to cause hypothyroidism alone. Serum total iodine levels measured during the hypothyroidal state in both cases were definitely elevated, and the perchlorate discharge test of both cases showed positive discharge (24 and 34%, respectively). The thyroid functions normalized after iodine restriction in the first case and initiating hemodialysis in the second case, in parallel with normalization of serum total iodine levels. These findings suggest that impaired renal handling of iodine resulting in elevation of serum iodine levels, rather than an autoimmune mechanism or extravascular hormone loss, played a principal role in the development of primary hypothyroidism found in these 2 patients, probably through a prolonged Wolff-Chaikoff effect.

Key words: Diabetes mellitus, Nephrotic syndrome, Hypothyroidism, Iodine organification defect

(Diabetic Nephropathy is clinically defined by persistent proteinuria in diabetic patients with concomitant advanced retinopathy. The degree of proteinuria is usually in the subnephrotic range, but heavy protein excretion and nephrotic syndrome may occur. The diabetic nephrotic state has been related to development of anasarcan status and to a poorer renal outcome [1]. In diabetic renal failure, anasarca may occur earlier than in non-diabetic renal failure, even in the absence of hypoalbuminuria [2], which partially accounts for the earlier requirement of hemodialysis. Variable contributions to this status of cardiac insufficiency and of vasomotor defects secondary to diabetic neuropathy and peripheral vascular disease have been recognized. However, the etiology that plays a major role in accelerating extravascular fluid retention has yet to be elucidated.

Hypothyroidism is commonly associated with extravascular fluid retention through increased capillary transudation of protein associated with decreased cardiac output and renal blood flow [3]. Therefore, deterioration of the anasarcan status may occur when hypothyroidism develops in cases showing a preexisting nephrotic state. We reported here, 2 diabetic cases of nephrotic syndrome due to advanced diabetic nephropathy complicated by non-autoimmune primary hypothyroidism, in which hypothyroidism developed along with deterioration of the anasarcan status and was likely caused by an intrathyroidal iodine organification defect.)
Materials and Methods

T4 and T3 concentrations in serum, urine and ascites were measured by an enhanced chemiluminescent assay (Chemilumi ACS-T4, Chemilumi ACS-T3, Chylone, respectively). Free T4, free T3 and TSH concentrations in serum, urine and ascites were measured by an enhanced chemiluminescent assay (Amerlite TSH-30, Amerlite-MAB FT4, Amerlite-MAB FT3, Amerlite TSH-30, Ohso Clinical Diagnostics, respectively). Serum reverse T3 concentrations were measured by the polyethylene glycol method. Anti-thyroid peroxidase (TPO) and antithyroglobulin antibody were determined by RIA (TPOAb ‘Cosmic’, TgAb ‘Cosmic’, Cosmic Corporation, respectively). Anti-TSH receptor antibody (TRAb) was measured by a radioreceptor assay (TRAb ‘Deido’, Deido). Normal ranges measured by these analysis were as follows: TPOAb, <0.3 U/ml; TgAb, <0.3 U/ml; TRAb, <10%. Serum total iodine and protein-binding iodine (PBI) levels were measured by ICP-MS analysis [4]. Normal ranges measured by this analysis were as follows: total iodine level, 40-90 μg/dl; PBI, 40-80 μg/dl.

The technetium images of the thyroid were obtained 20 min after injection of 3 mCi technetium-99 m pertechnetate. The normal range of the uptake was 0.4-3.0%. The iodine-perchlorate discharge tests were carried out after iodine-rich foods were restricted for at least 2 weeks. Thyroidal uptake was initially determined 3 h after 500 μg potassium iodine together with 200 μCi 123I (initial uptake) was administered. Then, 1.0 g sodium perchlorate (NaClO4) was given orally, and thyroidal uptake was measured again 1 h later (final uptake).

The change in 123I uptake was calculated as follows: [(initial uptake – final uptake)/initial uptake] × 100 = discharge rate (%). A discharge rate of more than 20% was considered positive.

Case Reports

Case one

The first patient, a 65-year-old Japanese female, was diagnosed with diabetes mellitus and hypertension at the age of 53 at a local hospital. Her glycemic control was very poor with elevated glycohemoglobin A1C (HbA1C) above 9%, despite treatment with 12.1U/day of intermediate insulin (Humalin N) s.c. daily since 56 years of age, probably due to non-compliance with dietary restriction.

At the age of 58, diabetic proliferative retinopathy was detected by an eye fundus examination, for which photocoagulation therapy was conducted at the same hospital. Since she gradually developed facial and pretibial edema accompanied by increasing malaise and dyspnea after age 65, she first consulted our hospital on April 28, 1995, and was admitted under a diagnosis of diabetes mellitus complicated by advanced diabetic triopathy. She had no serious past illnesses. Her father died of a heart attack in old age and her mother also had diabetes and died of an unknown cause at the age of 62. She had eaten iodine-rich foods, such as seaweed, since she was diagnosed as having diabetes.

Physical examination on admission revealed that she was 145 cm in height and 63 kg in weight (BMI: 30.0 kg/m²). Her temperature was 35.8°C and her pulse rate 92 beats/min. She showed a puffy face and pitting pretibial edema. On auscultation of the chest, respiratory sounds in the right lower portion of the lung were decreased. She had no palpable goiter. Areflexia of the Achilles tendon and loss of vibratory sense were noted.

Urinalysis on admission revealed massive glycosuria (55 g/day) and proteinuria (4.5 g/day). HbA1c (12.6%; normal range 4-6%) and fructosamine (322 μmol/l; 205-285 μmol/l) levels were both elevated. Despite normal levels of serum urea nitrogen (15.2 mg/dl; 8.0-20.0) and creatinine (0.6 mg/dl; 0.8-1.3), a decreased total protein (5.5 g/dl; 6.5-8.2) including albumin (2.8 g/dl; 3.7-5.5) level combined with increased lipid profiles such as serum total cholesterol (296 mg/dl; 150-219) and triglyceride (448 mg/dl; 30-170) levels suggested complicated nephrotic syndrome originating from advanced diabetic nephropathy. This was confirmed histologically by renal biopsied specimens obtained thereafter. Thyroid function tests on admission showed decreased FT4 (0.75 ng/dl; 0.85-1.72) and FT3 levels (2.0 pg/dl; 2.31-4.07) accompanied by elevated TSH levels (34.5 μU/ml; 0.32-4.57), indicating coexistence of mild primary hypothyroidism. Reverse T3 levels (250 μg/ml) were within the normal range (140-410 pg/ml). She was nega-
tive for TPOAb, TgAb, and TRAb (0.3 > U/ml, 0.3 >
U/ml and 4.2%, respectively). Ultrasonography
revealed normal size and echogenicity of the thyroid.
Chest X ray showed moderate retention of pleural
effusion in the right lung accompanied by mild
cardiomegaly (cardiothoracic ratio was 58%). Com-
puted tomography of the abdomen demonstrated
moderate retention of ascites (Fig. 1).

The clinical course after admission is shown in
Fig. 1. Ascites and right pleural effusion were grad-
ually decreased after starting peroral administration
of diuretics such as furosemide (40 mg/day) and
spironolactone (50 mg/day) in combination with salt
restriction (7 g/day) and bed rest. After initiating T4
replacement therapy in August 1995 (100 µg/day),
thyroid function normalized. However, in May
1996, reappearance of ascites and pleural effusion
were recognized along with a gradual increase in se-
rum creatinine level from 1.2 mg/dl to 4.0 mg/dl,
although a stable dose of diuretics was continuously
prescribed. Other factors potentially developing
anasarcous status such as novel cardiac or liver dys-
function were excluded based on stable left-ventricu-
lar wall motion on ultracardiographic examination
and normal liver function tests.

Concurrently, on January 1998, primary hypo-
thyroidism (FT4 0.65 ng/dl; FT3 1.75 pg/dl; TSH
45.5 µU/ml) reappeared despite continuation of the
initial dose of T4. During this period, the total
protein level was further decreased to 4.6 g/dl, ac-
companied by a concurrent decrease in the serum
albumin level (2.4 g/dl). In February 1998, iodine
restriction was initiated without alternating the dose
of T4 because serum total iodine levels measured at

Fig. 1. Clinical course and laboratory findings of the first case. Ascites and pleural effusion gradually regressed after starting
diuretic therapy. Thyroid function normalized after initiating oral T4 (100 µg/ day) in August 1995. However, in May
1996, reappearance of anasarcous status was recognized along with gradual increase in the serum creatinine level from
1.2 mg/dl to 4.0 mg/dl and reappearance of primary hypothyroidism. After initiating iodine restriction due to elevated
serum total iodine level (202 µg/dl) in February 1998 without alternating the dose of T4, anasarcous status again regressed
along with normalization of the thyroid hormone and serum total iodine level (75 µg/dl). BW, body weight; Cr., serum
creatinine level.
that time were clearly elevated (202 μg/dl). After initiating iodine restriction, ascites and right pleural effusion again regressed along with normalization of the thyroid hormone level, while the serum creatinine level further increased to 5.0 mg/dl. During this period, total protein level was slightly elevated to 5.1 g/dl, accompanied by concurrent increase in serum albumin level (2.7 g/dl). Thereafter, a normal thyroid hormone level was maintained with minimal ascetic retention. Finally, serum total iodine levels measured in February 1999 were within the normal range (75 μg/dl).

Case two

The second patient, a 50-year-old Japanese male, first consulted Kyoto City Hospital on April 20, 1995, complaining of thirst which had progressively developed since February 1995. He was diagnosed with diabetes mellitus complicated by advanced triopathy, based on fasting hyperglycemia (270 mg/dl), diabetic proliferative retinopathy on eye fundus examination and overt proteinuria (2.5 g /day). Glycemic control was poor with elevated glycohemoglobin A1C (HbA1C) above 8%, despite treatment with 6 IU/day of intermediate insulin (Penfill N) s.c. daily since the first hospital visit. Since he gradually developed abdominal distention and pretibial edema accompanied by an increase in serum creatinine level around 3 mg/dl, he consulted our hospital and was admitted on June 29, 1995. He had no serious past illnesses and no family history of diabetes. Moreover, he had not taken excess iodine.

Physical examination on admission revealed that

![Abdominal CT](image)

Fig. 2. Clinical course and laboratory findings of the second case. Ascites gradually regressed after diuretic therapy. However, serum creatinine levels gradually increased to over 8.4 mg/dl in accordance with the severe anasarcous status and gradual progression to severe primary hypothyroidism, despite initiating oral T4 (100 μg/ day) in November 1998. Serum total iodine levels measured at that time (220 μg/dl) were clearly elevated. After starting hemodialysis on December 4, 1998, the anasarcous status rapidly regressed in accordance with normalization of thyroid hormone level and serum iodine level (75 μg/dl). Finally, after discontinuation of the oral T4 on April 21, 1999, thyroid hormone levels have been well maintained within normal ranges. HD, hemodialysis.
he was 174 cm in height and 87.5 kg in weight (BMI: 28.9 kg/m²). His temperature was 36.0°C and his pulse rate 84 beats/min. The thyroid gland was not palpable. There was no cardiac murmur or rales heard on the chest. The abdomen was distended and pitting pretibial edema was noted. Areflexia of the Achilles tendon and loss of vibratory sense were noted.

Urinalysis on admission revealed massive glycosuria (34 g/day) and proteinuria (15.7 g/day). Both HbA1c (4.8%) and fructosamine (125 μmol/l) levels were decreased compared to the normal ranges. In addition to the proteinuria accompanied by an increase in serum urea nitrogen (41.2 mg/dl) and creatinine (3.8 mg/dl) levels, a decreased total protein (4.1 g/dl) including albumin (1.8 g/dl) level combined with increased lipid profiles such as serum total cholesterol (242 mg/dl) and triglyceride (228 mg/dl) levels suggested complicated nephrotic syndrome originating from advanced diabetic nephropathy. Thyroid function tests on admission showed normal FT4 (1.34 ng/dl) and FT3 levels (2.99 pg/dl) accompanied by elevated TSH levels (11.7 μU/ml), indicating coexistence of subclinical hypothyroidism. Reverse T3 levels (179 pg/ml) were within the normal range. He showed negative TPOAb, TgAb and TRAb (0.4 U/ml, 0.4 U/ml and 2.4%, respectively). Thyroid echography revealed normal size and echogenecity of the thyroid. Chest X-ray showed mild cardiomegaly (cardiothoracic ratio was 52%) accompanied by mild pleural effusion in the bilateral lungs. Computed tomography of the abdomen demonstrated moderate retention of ascites (Fig. 2).

The clinical course after admission is shown in Fig. 2. Ascites gradually regressed after peroral administration of furosemide (40 mg/day) combined with salt restriction (5 g/day) and bed rest. However, serum creatinine levels gradually increased to over 5.0 mg/dl in accordance with a decrease in FT3 and FT4 levels associated with a gradual increase in the TSH level, indicating progression to overt primary hypothyroidism. Since October 1998, a severe anasarca state including massive ascites and pleural effusion developed when the maximal serum creatinine level was 8.4 mg/dl and thyroid function deteriorated to severe hypothyroid status on December 2, 1998 (FT4 0.43 ng/dl; FT3 1.42 pg/dl; TSH 257.0 μU/ml), despite initiating T4 replacement therapy (100 μg/ day) in November 1998. Other factors potentially developing anasarca status such as novel cardiac or liver dysfunction were excluded based on stable left-ventricular wall motion on ultracardiographic examination and normal liver function tests.

Serum total iodine levels measured at that time (220 μg/dl) were clearly elevated. Therefore, on December 4, 1998, hemodialysis combined with T4 replacement therapy were initiated. After starting hemodialysis, the volume of ascites and pleural effusion rapidly regressed, while serum creatinine levels decreased to approximately 5.0 mg/dl. Since February 1999, the thyroid hormone level increased to the normal range, and serum total iodine levels measured on February 22, 1999 (75 μg/dl) were within the normal range. Since March 20, tapering of T4

Fig. 3. Histological examinations of the thyroid gland performed during the hypothyroidal phase in our 2 cases (hematoxylin-eosin, × 50). A: Specimen of the first case reveals almost normal thyroid follicles without lymphocytic infiltration. B: Specimen of the second case reveals relatively large follicles with cuboidal epithelial cells without lymphocytic infiltration.
replacement was initiated because the TSH level was suppressed to under the normal range. Finally, after discontinuation of the oral T4 since April 21, the thyroid hormone level were well maintained within normal ranges.

**Histological examinations (Fig. 3) and scintigraphic studies**

Histological examinations of the thyroid gland (Fig. 3) in the 2 cases studied during the hypothyroidal phase revealed almost normal thyroid follicles without lymphocytic infiltration or amyloid deposition. However, relatively large follicles with cuboidal epithelial cells were observed in the second patient (lower panel in Fig. 3). Scintigraphy with technetium-99m revealed normal uptake in both patients (1.48% in the first case; 1.65% in the second case). Perchlorate discharge test performed in both patients revealed definite positive discharge (24 and 34%, respectively), suggesting an intrathyroidal iodine organification defect.

**Measurement of thyroid hormone levels in the urine and ascites**

Mean T3, T4, FT3 and FT4 levels measured on 2 consecutive days during the hypothyroidal phase in the urine from the 2 patients were 0.9 µg/day, 25 µg/day, 0.9 ng/day and 11 ng/day, respectively, in the first case, and 0.3 µg/day, 10 µg/day, 0.4 ng/day and 3 ng/day, respectively, in the second case. Similarly, mean T3, T4, FT3 and FT4 concentrations in ascites from the 2 patients were 74 µg/dl, 6.4 µg/dl, 1.3 pg/ml and 11 ng/dl, respectively, in the first case, 30 µg/dl, 1.0 µg/dl, 0.4 pg/ml and 0.3 ng/dl, respectively, in the second case. Based on the assumption that the production of ascites was 1 liter per day, loss of thyroxine and triiodothyronine into the urine and ascites was estimated to be 69 µg/day and 1.6 µg/day, respectively, in the first case, and 11 µg/day and 0.6 µg/day, respectively, in the second case. Since it was estimated that average normal secretion in euthyroid humans ranges from 94 to 110 µg T4 and from 10 to 22 µg T3 [5, 6], the amounts of thyroid hormone lost into the extravascular space alone such as that in urine and ascites may not have been sufficient to cause hypothyroidism.

**Discussion**

The association between renal dysfunction and thyroid function has been extensively studied, especially in patients with chronic renal failure [7-11], and were recently reviewed in detail by Kaptein [12]. In general, reduced serum thyroid hormone levels with almost normal TSH levels, common to other non-thyroidal illnesses, and an increased prevalence of goiter have been reported. Even in nephrotic syndrome with decreased total T3 and T4 levels, serum free T4 and TSH levels remain within normal limits [13], except in patients with congenital or grave nephrotic syndrome with markedly increased urinary loss of thyroid hormone potentially developing true hypothyroidism [14, 15]. There is no evidence that renal dysfunction itself has a direct inhibitory effect on thyroid function.

However, decreased serum free T4 and T3 levels accompanied by markedly elevated TSH and normal reverse T3 levels observed in our 2 cases complicated by advanced diabetic nephropathy indicated the coexistence of not non-thyroidal illness but true primary hypothyroidism [12]. In these 2 cases, antithyroid antibody was negative, and histological examination of the thyroid gland revealed almost normal thyroid follicles without interstitial lymphocytic infiltration. Therefore, an autoimmunological abnormality, such as Hashimoto’s autoimmune thyroiditis, was not the precipitating factor for primary hypothyroidism found in these 2 cases. However, the amounts of thyroid hormone lost to the extravascular space such as in urine and ascites were not sufficient to cause hypothyroidism alone as previously reported in congenital nephrotic syndrome or grave nephrotic syndrome [14, 15].

An important finding observed in our 2 patients was the elevated serum total iodine levels during the hypothyroidal state, which were 202 and 220 µg/l, respectively. The Wolff-Chaikoff effect, an iodine-induced block of iodine organification, was reported to be observed when the serum inorganic iodine level was above 50-350 µg/l in humans [16] or in experimental animals [17]. Therefore, the excess serum iodine observed in our 2 cases may have been responsible for the development of hypothyroidism through the Wolff-Chaikoff effect. However, predisposition of the thyroid gland seems to be a
prerequisite for failure to escape from the inhibitory effect of excess iodine, because not all patients with elevated serum non-hormonal iodine levels develop hypothyroidism [18]. A prolonged inhibitory effect of iodine has already been reported in nephrectomized rats by Wolff and Chaikoff [19]. Their study suggests that some patients with renal dysfunction are susceptible to iodine-induced reversible hypothyroidism without immunological perturbation. In our 2 cases, the defect in organification of iodine was confirmed by a positive perchloride discharge test performed at the hypothyroid phase in both cases (24 and 34%, respectively). Moreover clinically, the thyroid function normalized after only iodine restriction in the first case and initiating hemodialysis in the second case, which was reported to clear iodine 4–5 times higher than the endogenous renal clearance of the ion [20], in accordance with normalization of serum total iodine levels. Especially, in the second case, after discontinuation of the T4 replacement, the thyroid hormone levels were still maintained within normal ranges, indicating that the hypothyroidism was completely reversible. Very interestingly, the anasarous status ameliorated in accordance with normalization of the thyroid hormone level in both cases. Certainly, in the first case, slight increases in both serum protein and albumin levels were observed after iodine restriction. However, it should be estimated that normalization of thyroid hormone level after iodine restriction mainly induced the amelioration of the anasarous status through decreased capillary transduction of protein with increased cardiac output resulting in an increase in both serum protein and albumin levels regardless of progressively decreased renal function.

Recently, Takeda et al. [21] reported 3 cases on regular dialysis treatment accompanied by iodine-induced reversible hypothyroidism and the overall prevalence of this condition among patients on regular hemodialysis or continuous ambulatory peritoneal dialysis was 3.2% (3/93). Furthermore, Sato et al. [18] reported that among 245 patients with primary hypothyroidism (serum TSH > 10 mU/l), 36 patients were associated with renal dysfunction which was defined as the serum creatinine level >106 μmol/l. Recovery of thyroid function after iodine restriction in these patients was observed in 30 (83%), in whom an elevated serum non-hormonal iodine level (median 236, range 67–15591 μg/l, N=19) was observed. The perchlorate discharge test was positive, and an almost normal thyroid gland was confirmed histologically in 8 patients as shown in our cases. They postulated that impaired renal handling of iodine demonstrated through potassium iodide loading test rather than an autoimmune mechanism plays a significant role in the pathogenesis of reversible hypothyroidism associated with renal dysfunction, potentially through a prolonged Wolff-Chaikoff effect. However, the etiologies of renal dysfunction with hypothyroidism described in these studies [18, 21] did not include diabetic glomerulosclerosis, but mainly included chronic glomerulonephritis.

Corvilain et al. [22] reported that excess iodine inhibited the action of intrathyroidal cellular signals on an H2O2 generating system, which is a main precipitating factor for iodine organification, developing Wolff-Chaikoff effect. Previous reports demonstrated H2O2 production stimulated by granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, opsonized zymosan and so on in neutrophils [23] and monocytes [24] from diabetic patients were significantly decreased compared with those from non-diabetic controls, but it is still not clear whether H2O2 production stimulated by excess iodine in thyrocytes from diabetic patients was decreased in vivo or in vitro. Therefore, the prevalence of the development of non-autoimmune hypothyroidism among diabetic patients complicated by advanced nephropathy must be elucidated based on controlled clinical study using greater numbers of diabetic and non-diabetic patients in the future.

In summary, we reported 2 diabetic patients complicated by nephrotic syndrome due to advanced diabetic nephropathy who demonstrated primary hypothyroidism. Clinical and laboratory findings suggest that impaired renal handling of iodine due to excess serum iodine rather than an autoimmune mechanism or extravascular hormone loss plays a principal role in the development of this condition, probably through a prolonged Wolff-Chaikoff effect.

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References