Case Report

Renal dysfunction manifesting in subclinical hypothyroidism—a possible role for Thyroxine

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Abstract
Renal dysfunction, both acute and chronic, is a recognized association of overt hypothyroidism. We describe a patient who developed renal dysfunction at the stage of subclinical hypothyroidism. We emphasize that renal dysfunction is a reflection of tissue hypothyroidism, dissociated with the severity of biochemical hypothyroidism and can manifest in patients with subclinical hypothyroidism. This report also makes a case for thyroxine therapy if an alternative cause of renal dysfunction is not found in a patient with subclinical hypothyroidism.

Keywords: chronic kidney disease; hypothyroidism; renal dysfunction; subclinical hypothyroidism

Background
Renal manifestations of hypothyroidism can be quite similar to those seen in patients with intrinsic renal disease. Hence, it has been recommended that thyroid function is assessed in patients with otherwise unexplained renal dysfunction before resorting to invasive investigations like renal biopsy [1]. Though glomerular and tubular function is influenced by thyroid status, it is very unusual to have a significant rise in serum creatinine (SCr) in patients with subclinical hypothyroidism (SCH) [2].

Case presentation
A 57-year-old Asian man was referred from a private clinic for investigation of renal impairment. His only complaints were those of fatigue and mild aches and pains in the limbs. He was diagnosed with hypertension 1 month earlier, but there was no history of diabetes mellitus, heart disease, nephrolithiasis or urinary tract infections. His medication included hydrochlorothiazide, 12.5 mg once daily, and multivitamins. He denied chronic use of non-steroidal anti-inflammatory drugs or herbal medication. One of his sisters had been treated for a thyroid disorder, but there was no family history of renal disease. Two years earlier, a pre-employment health check at another institution had revealed SCH, positive anti-thyroid antibodies, hypercholesterolemia and renal dysfunction (Table 1; time ‘−2 years’). There was no proteinuria and renal tract ultrasound was unremarkable. Sustained rise of SCr over a period of 4 months in the absence of a recognizable cause of renal dysfunction had led to a renal biopsy. However, it did not show any abnormalities on light microscopy or immunofluorescence; electron microscopy was not performed.

Physical examination showed a blood pressure of 135/75 mmHg but no oedema, muscle tenderness, skin rash, arthritis, lymphadenopathy, organomegaly or goitre. Laboratory investigations confirmed renal dysfunction with SCr of 175 μmol/L and estimated glomerular filtration rate according to the four-variable Modification of Diet in Renal Disease Study equation (MDRD eGFR) of 35 ml/min/1.73 m² (Table 1; time ‘0’). Urinary protein excretion was normal at 0.07 g/day. Urinalysis did not show haematuria, pyuria, bacteriuria or myoglobinuria. A renal ultrasound demonstrated normal-sized unobstructed kidneys. Anti-nuclear antibody was negative and serum complement levels were within the normal limits.

Thyroid function tests revealed markedly raised serum thyroid-stimulating hormone (TSH) and low serum free thyroxine (FT4) levels. Anti-thyroid peroxidase antibodies were positive. Serum lipid profile showed high total and LDL cholesterol. Serum creatine kinase was normal.

A diagnosis of overt hypothyroidism secondary to autoimmune thyroiditis was made. Renal dysfunction was felt to be a reflection of hypothyroidism and thyroxine replacement therapy was initiated; renal biopsy was not repeated. Subsequent follow-up demonstrated normalization of thyroid hormone levels with concomitant improvement in renal function and serum cholesterol levels (Table 1; time ‘+1 to +3 years’). Most of this improvement was seen within the first year though continuing improvement was still noticeable during the succeeding 2 years. After 3 years of thyroxine treatment, his SCr has decreased to 103 μmol/L, translating into the MDRD eGFR of 68 ml/min/1.73 m². It is fascinating that this level of renal function is strikingly better than that seen at the stage of SCH (SCr 150 μmol/L; MDRD eGFR 42 ml/min/1.73 m²) 5 years earlier. Similarly, though
his hypercholesterolaemia eventually required statin treatment, it is remarkable that the levels of serum total and LDL cholesterol after achieving euthyroidism were significantly lower than those at the SCH stage.

### Discussion

We describe a patient who was assessed for renal dysfunction at two different evolutional stages of hypothyroidism—SCH (high serum TSH but normal FT4 level) and overt hypothyroidism (high serum TSH and low FT4 level). He had no long-standing risk factors for chronic kidney disease. On both occasions, increase in SCr was not associated with abnormal urinalysis or urinary tract obstruction, implying the presence of pre-renal insufficiency rather than an intrinsic renal disease. As it is unusual for SCH to cause clinically significant renal dysfunction, a renal biopsy had been carried out in the past after documentation of persistent but ‘unexplained’ increase in SCr over several months. However, it failed to reveal any pathological lesions. A therapeutic trial of thyroxine was not given at that time.

By the time of his second medical encounter 2 years later, both the hypothyroidism and renal dysfunction had progressed. In view of overt hypothyroidism, absence of an alternative explanation of renal dysfunction and previous normal renal histology, the possibility of renal dysfunction secondary to hypothyroidism was entertained. Achievement of euthyroidism by thyroxine treatment was coupled with marked improvement in renal function which further pointed to ‘functional’ impairment rather than irreversible histologic damage as a cause of renal dysfunction in our patient. It is plausible to assume that the rise in his SCr

### Table 1. Laboratory values before and after thyroxine treatment

| Time       | - 2 years | 0   | + 1 year | + 2 years | + 3 years |
|------------|-----------|-----|----------|-----------|-----------|
| **TSH (mU/L)** | 14        | >100| 4.3      | 3.8       | 0.5       |
| **FT4 (pmol/L)** | 13        | -5.2| 15.1     | 11.8      | 14.2      |
| **SCr (µmol/L)** | 150       | 175 | 118      | 110       | 103       |
| **eGFR (ml/min/1.73 m²)** | 42        | 35  | 55       | 59        | 64        |
| **Cholesterol (mmol/L)** | 7.5       | 9.4 | 6.3      | 6         | 4.8<sup>a</sup> |
| **LDL (mmol/L)** | 5.8       | 6.7 | 3.9      | 4         | 2.5<sup>a</sup> |

TSH, thyroid-stimulating hormone; FT4, serum free thyroxine; SCr, serum creatinine; eGFR, estimated glomerular filtration rate (four-variable Modification of Diet in Renal Disease Study equation).

<sup>a</sup>On treatment with statins.
represented reduction in GFR and, possibly, decrease in tubular secretion of creatinine—a process mediated by the thyroid hormones via the Na\(^+\)-Ca\(^{2+}\) exchanger and the Na\(^+\)-K\(^+\) ATPase activity [3]. Normal serum creatine kinase and absence of myoglobinuria ruled out myopathy/rhabdomyolysis as a cause of increased SCr.

The finding of increased SCr at a stage when serum T4 level was normal is intriguing as SCH rarely produces clinically significant renal effects. It is noteworthy that all the patients with hypothyroidism-related renal dysfunction described by Connor et al. [1], Mooraki et al. [4], Silva et al. [5] and Van Welsem et al. [6] had overt hypothyroidism. Nevertheless, considering the adverse cardiac consequences of SCH, the concept of renal dysfunction in SCH is not entirely inconceivable. Improvement in myocardial contractility with thyroxine replacement in such patients can enhance renal blood flow and GFR [7–9].

In an analysis of patients with varying degrees of hypothyroidism, Zulewski et al. highlighted the discordance between biochemical and clinical hypothyroidism so that some patients with severe biochemical hypothyroidism had only mild clinical manifestations, whereas other patients with trivial biochemical changes had quite severe physical signs and symptoms [10]. In the same fashion, it appears that there can also be a complete dissociation between the severity of biochemical hypothyroidism and its target organ/tissue manifestations. It is our perception that increased SCr and cholesterol levels at the SCH stage in our patient represented tissue hypothyroidism. Absence of laboratory/histological evidence of an alternative pathology for renal dysfunction and improvement in renal abnormalities and serum cholesterol with thyroxine treatment to levels below those seen at the SCH stage give strength to our hypothesis.

In view of a positive family history of thyroid disease, positive anti-thyroid antibodies as well as a serum TSH level of >10 mU/L, he was a high-risk patient for progression to overt hypothyroidism. Treatment with thyroxine at the stage of SCH would have prevented progression to overt hypothyroidism and corrected the metabolic abnormalities at an earlier stage.

**Conclusion**

This report illustrates that renal dysfunction can be seen across the whole spectrum of severity of hypothyroidism—including SCH. It also raises the possibility of clinical usefulness of thyroxine in the treatment of renal dysfunction associated with SCH (after a careful exclusion of other aetiologies of renal impairment). Further clinical research is needed to examine the role of thyroxine in this clinical scenario.

**Conflict of interest statement.** None declared.

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