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REVIEW ARTICLE

Hypothyroidism and Nephrotic Syndrome: Why, When and How to Treat

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Abstract: Hypothyroidism, characterised by low/normal free thyroxine (FT_4) and free tri-iodothyronine (FT_3) with elevated thyroid-stimulating hormone (TSH), is a well-known complication of nephrotic syndrome (NS). This is a common feature of primary and secondary glomerular diseases and comprises loss of protein in the urine and increased urinary excretion of thyroid hormones and thyroxine-binding globulin. With a normal thyroid reserve, this scenario is associated with the development of subclinical hypothyroidism, with a slight increase in TSH and normal free fractions. However, with a low thyroid reserve the transition toward overt hypothyroidism is almost inevitable, affecting morbidity and mortality. As T4 replacement is a cheap and well-established treatment to achieve a stable hormone status in different types of thyroid deficiency, it is essential to recognise and appropriately treat this condition. In this article we summarise the evidence on this nephro-endocrine disorder in humans and focus on diagnostic and therapeutic strategies.

Keywords: Nephrotic syndrome, hypothyroidism, glomerulonephritis, thyroid hormones, replacement.

INTRODUCTION

Despite the considerable available data, the exact prevalence of hypothyroidism and subclinical hypothyroidism in adult patients with nephrotic proteinuria is still unclear [1]. Surprisingly, the 2012 clinical practice guidelines for glomerulonephritis do not mention hypothyroidism as a complication of glomerular disease [2], leading to a risk of its serious underdiagnosis. However, the latest American guidelines for the treatment of hypothyroidism underline the role of severe urinary protein loss in increasing replacement therapy requirements [3]. For these reasons, this review focuses on the most recent evidence and information on this topic.

PATHOPHYSIOLOGY

The hypothalamic-pituitary-thyroid axis is a complex endocrine system which controls the production of thyroid hormones. The paraventricular nucleus of the hypothalamus secretes thyrotropin-releasing hormone, which in turn leads to pituitary secretion of thyroid-stimulating hormone (TSH). TSH binds to thyroid receptors and stimulates the biosynthesis and secretion of thyroxine (T_4) and tri-iodothyronine (T_3) into the plasma [4]. The steps involved are: (i) transport of iodine into the thyroid gland; (ii) iodination of thyroglobulin tyrosyl residues, resulting in synthesis of either monoiodinated tyrosine (MIT) or di-iodinated tyrosine (DIT), incorporated into thyroglobulin; (iii) coupling of iodotyrosines to form the hormonally active iodothyronines: two DITs lead to the formation of T_4, while one DIT plus one MIT lead to T_3 synthesis.

The hormones thus formed are held in thyroglobulin, the major component of intrafollicular colloid. The active thyroid hormones free T_3 (FT_3) and free T_4 (FT_4) are released through the hydrolysis of thyroglobulin by a thyroid protease and peptidases [5]. About 85 μg of T_4 are secreted by the thyroid gland every day, while only 20% of the 33 μg of normally circulating T_3 derives from direct thyroid release. The rest (80%) is produced by a peripheral T_4 deiodination reaction involving a specific enzyme which removes one iodine from the outer ring of T_4 [6]. Thyroid hormones are linked with the plasma binding proteins thyroxine-binding globulin (TBG), transthyretin and human serum albumin during transport; these account, respectively, for 74, 11 and 15% of all T_4 binding. The high affinities of the binding proteins result in a slow clearance and prolonged half-life of thyroid hormones in the circulation [7].

Upon release to the target tissues through different carriers, thyroid hormones undergo cytosolic enzymatic reactions, involving T_4 deiodination by iodothyronine deiodinases (types 1, 2 and 3) [8]. The selective removal of an iodine atom from the phenolic (outer) ring produces the biologically active hormone T_3, whereas its removal from the tyrosyl (inner) ring generates the inactive metabolite reverse T_3. These reactions play a crucial role in the homeostasis of thyroid hormones [4]. The final step of this cascade is the

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interaction between active hormones and their nuclear thyroid hormone receptors, which modulates gene transcription in response to hormones [9].

While hypothyroidism is defined as high serum TSH with concomitant low levels of FT_3 and FT_4, subclinical hypothyroidism involves elevated TSH despite normal serum levels of FT_3 and FT_4 [10]. The American Association of Clinical Endocrinologists/American Thyroid Association recommends treating the latter condition only in symptomatic patients positive for thyroid antibodies or with cardiovascular risk factors [3]. There are no clinical outcome data supporting levothyroxine (LT_4) treatment in patients with serum TSH levels between 2.5 and 4.5 mIU/L [3]. It is recommended that all patients with subclinical hypothyroidism and a TSH >10 mIU/L be treated with LT_4, as they have higher all-cause mortality [11]. Hypothyroidism and moderate subclinical hypothyroidism are associated with increased all-cause mortality independent of coronary heart disease [11] and with increased risk of heart failure [12].

According to most recent guidelines, NS in adults is defined as a complex alteration of the glomerular filtration barrier which results in proteinuria >3.5 g/24 h, hypoalbuminaemia (<3 g/dL), peripheral oedema and often hyperlipidaemia. Heavy proteinuria (>3.5 g/24 h) without the clinical features of NS is commonly referred to as isolated nephrotic proteinuria [2]. This specific presentation of kidney disease may occur in a wide variety of primary and systemic diseases and its incidence is estimated to be three new cases per 100 000 each year [13]. In adults, the main causes seem to be primary glomerulonephritis (in particular membranous nephropathy and focal segmental glomerulosclerosis), while approximately 30% of cases are due to a systemic disease such as diabetes mellitus, systemic lupus erythematosus or amyloidosis [14-17]. Complications in NS may be part of the disease itself or develop as a consequence of its treatment [18]. The loss of proteins in the urine changes their plasma concentrations, causing secondary insufficiency and impairment of metabolic functions [19].

Abnormal thyroid function is a not uncommon complication of nephrotic diseases. Its pathophysiology was first investigated in 1926, when Albert A. Epstein postulated a common aetiology for hypothyroidism and nephrotic state [20]. It was later clarified that LT_4 is ineffective in the treatment of proteinuric diseases and that hypercholesterolaemia in nephrosis is not only related to hypothyroidism, but above all to the urinary loss of lipoprotein binding proteins [21, 22]. In fact, although the exact cause appears to be complex, dysthyroidism in NS has been explained by the loss of hormone binding proteins occurring in this setting [23]. The large fraction of thyroid hormones bound to plasma proteins pass the glomerular filtration barrier and are lost in urine, as they are only partly reabsorbed in the proximal tubule by megalin and cubilin complexes [24]. The progressive tubular defect typically seen in chronic proteinuric diseases may then exacerbate the pre-existing decline of circulating thyroid hormone.

Small observational studies of the renal metabolism of FT_3 and FT_4 conducted in healthy subjects have demonstrated that FT_4 is usually mostly reabsorbed by the tubules, while FT_3 is just secreted [25, 26]. A tubular dysfunction may therefore affect FT_3 and FT_4 metabolism, worsening the primary glomerular insufficiency. Although evidence of urine excretion of T_4, T_3 and TBG in NS is limited, most studies have confirmed the high excretion of T_4 and T_3 during nephrosis [27]. Furthermore, there was a positive correlation between 24 h proteinuria and urinary concentration of T_4, T_3 and TBG in patients with NS, while serum TSH was negatively correlated with albumin [28]. In other words, the increase in TSH is correlated with the degree of proteinuria, and is thus a possible predictor of worsening kidney failure [1]. Furthermore, in some clinical trials hypothyroidism was associated with oedema onset and there was a remission of protein loss upon relief of the hypothyroidism [29]. However, as recent literature confirms, most patients with NS have subclinical hypothyroidism, with normal FT_3 and FT_4 levels and elevated TSH compared with basal values [30]. This indicates that the thyroid is normally able to compensate for the urinary loss of hormones and patients remain euthyroid. However, if a primary glandular disease coexists, overt hypothyroidism can develop, leading to an increase in exogenous levothyroxine requirements [31].

In any case, the hormonal thyroid profile in nephrotic states is highly variable and hypothyroidism is known to have different degrees of severity [32]. In consequence, dysthyroidism in nephrotic kidney diseases is likely to have a more complicated pathophysiology. In addition, TSH is a low molecular weight protein (28.5 kDa), which can be lost in urine in patients with glomerular disease. Increased urinary excretion of TSH has been reported in some small-caseload studies, suggesting another possible explanation for non-constant onset of hypothyroidism among these patients [33]. Obviously, the difference in proteinuria selectivity may itself further confuse the hormone profiles, producing different degrees of hypothyroidism in patients with different glomerulopathies [34]. Furthermore, it has already been shown that a lower T_3 level correlates with a higher urinary amount of T_4. This might be explained by a decreased peripheral conversion of T_4 to T_3, suggesting a possible reason for the various presentations [32].

The considerable impact of hypothyroidism in nephrotic diseases could also be related to the concomitant presence of any acute and/or chronic renal impairment. Elevated serum creatinine and reduced glomerular filtration rate have been associated with subclinical hypothyroidism [35]. The pathophysiological mechanisms underlying this association were thought to be the decline of renal plasma flow, promoted by the imbalance between stroke volume and peripheral resistance [36], hyperlipidaemia [37] and the effects of paracrine and endocrine mediators such as insulin-like growth factor type 1 and vascular endothelial growth factor [30]. Furthermore, an interconnection between thyroid dysfunction and renal impairment has been observed in several case series where complete remission of hypothyroidism was achieved only on reaching end stage renal disease [38, 39].

Another point to be clarified with regard to NS and dysthyroidism is the key role played by altered iodine metabolism in proteinuric diseases [40]. Briefly, non-autoimmune hypothyroidism in NS cannot be explained by the substantial urinary excretion of T_4, T_3 and TBG alone. An increased urinary concentration of thyroid hormones and

their carriers has been observed in various kinetic and clinical studies, demonstrating not only a correlation between hypothyroidism and the degree of nephrosis but also a close interconnection with the remission of these conditions. However, several other factors may influence the degree of dysthyroidism in this setting, including thyroid performance and factors influencing hormone biosynthesis, impairment of tubular function and the effect of kidney dysfunction on T_4-T_3 peripheral conversion.

WHY SCREENING FOR SUBCLINICAL HYPOTHYROIDISM SHOULD BE PERFORMED IN NS

The role of hypothyroidism in reducing the glomerular filtration rate, changing water homeostasis and, consequently, causing hyponatraemia is well known [30]. It is not uncommon that patients with thyroid hormone deficiency suffer from generalised oedema, primarily due to a reduction in free water clearance [41]. Similarly, oedema, essentially caused by sodium retention and a drop in plasma oncotic pressure, is a common clinical manifestation of NS [42]. Water retention normally worsens renal function in patients with primary glomerulonephritis and patients are usually asked to restrict their dietary fluid and sodium intake and take a diuretic therapy [43]. It is therefore very important to bear in mind that if a nephrotic glomerular disease is accompanied by hypothyroidism, the severe urinary loss of proteins may exacerbate fluid retention, which may be difficult to resolve if the treatment of hypothyroidism is delayed.

Finally, it has been demonstrated that normalising T_3 and T_4 concentrations with replacement therapy also preserves renal function in patients with a kidney disease and subclinical hypothyroidism, and is an independent predictor of renal outcome [44]. For this reason, even though there are no specific recommendations for thyroid screening in patients with NS, we suggest thyroid function be screened not only in patients with pre-existing thyroid disease but also in those with no history of dysthyroidism. Earlier identification of thyroid hormone abnormalities may improve the global management of nephropathic patients and their comorbidities. In particular, the close relation between hypothyroidism and cardiovascular disease has already been investigated. Thyroid hormones seem to have a direct action on myocardial and vascular function; they can influence endothelial dysfunction, blood pressure control and dyslipidaemia [45, 46]. Furthermore, thyroid deficiency is linked to abnormalities of cardiac myocytes and vascular smooth muscle cells and may interfere with the actions of cardiologic and lipid-lowering therapies [47].

WHEN A SUPPLEMENT THERAPY SHOULD BE CONSIDERED

The standard treatment for hypothyroidism is LT_4, thanks to its great efficacy, simple once-daily oral administration and fast resolution of the signs and symptoms of hypothyroidism in the majority of patients (in 6 weeks at most) [48]. However, the treatment fails to restore thyroid function in a small part (10-15%) of patients, for whom LT_3+LT_4 combination therapy is suggested.

Recent advances in the understanding of thyroid hormone physiology show that genetic variation in deiodinases [49] or in thyroid hormone transporters [50] may be partly responsible for this difference. The clinician's goals must be to resolve hypothyroid signs and symptoms and normalise serum thyroid hormone concentrations (TSH, FT_3 and FT_4, with TSH as the marker of replacement treatment adequacy) while avoiding overtreatment (iatrogenic thyrotoxicosis), especially in selected subpopulations (elderly, cardiopathic, etc.). An optimal and consistent absorption is achieved only when LT_4 is taken either 60 min before breakfast or at bedtime (3 or more hours after the evening meal) and preferably apart from other potentially interfering medications and supplements [51]. Co-administration with food is likely to impair levothyroxine absorption [52], but it is also important to consider patient adherence: although a fasting regimen may promote absorption, if administration 1 h before breakfast is unfeasible, 30 min before breakfast may also be reasonable.

The standard of choice of the minimum effective dose for hypothyroid patients could depend on various different factors, and should ideally be tailored to the patient: actual or ideal body weight, TSH goal, aetiology of hypothyroidism, degree of serum TSH elevation, pregnancy and age. The dose is generally calculated as 1.6 - 1.8 μg/kg of actual body weight [48, 53, 54]. In some cases, higher doses are required, especially in patients with little residual thyroid function [55]: from 2.0 - 2.1 μg/kg during primary hypothyroidism, after Basedow ablation or in athyreotic patients [56] to 2.1 - 2.7 μg/kg in patients with thyroid cancer [57]. Hypothyroid women taking LT4 typically require a dose increase early in the first trimester of pregnancy [58]. This challenge is required not only because of the well-known requirement for thyroid hormone to develop the fetus' neural tube, but also because of the increased risk of autoimmune kidney disease (e.g. glomerulonephritis) during this period [51].

The replacement LT_4 dose required to normalise TSH tends to decrease with age [53]. Experts advise 'starting low and going slow', especially in elderly patients and those with cardiovascular disease, to avoid precipitating cardiac events [59]. Generally, after initiation of the calculated dose, adjustments of 12.5 - 25 μg/day could be made, based on serum TSH. TSH should then be retested at 4 - 6 weeks and 4 - 6 months to enable dose adjustment as necessary, and then monitored yearly [51].

Unfortunately, as yet there are no clinical data on the initiation of replacement therapy with LT_4 in patients with NS and subclinical and/or overt hypothyroidism. In fact, although the latest American Thyroid Association guidelines suggest performing thyroid function assessment during NS, they lack any recommendations on dosing, timing and specific adjustments [60].

HOW CAN HYPOTHYROIDISM BE TREATED

LT_4 is generally prescribed worldwide in the form of tablets, although recent data suggest that gelatin capsules or oral liquid formulations may have a more favourable absorption profile in selected circumstances. Due to the lack of randomised controlled trials the use of these different preparations cannot currently be recommended. A switch to a gel capsule or liquid formulation might be worth considering in the rare event of putative allergies to excipients. An alterna-

tive approach when poor absorption is suspected is to increase the LT_4 tablet dose [51].

The gelatin capsule formulation contains liquid LT_4 [61] in contrast to standard solid LT_4 tablets: this enables fast, efficient dissolution, even at a low pH [62]. Some studies found that capsules are better absorbed when taken with coffee or proton pump inhibitors [63], allowing suppression of serum TSH in patients who did not reach euthyroidism with standard LT_4 tablets [64]. A retrospective uncontrolled trial described lower serum TSH concentrations when switching from tablets to soft gel capsules of the same dose of LT_4 [65].

A liquid LT_4 formulation has also been proposed. Recent data suggested that this formulation could be better absorbed than tablets in cases of malabsorption (e.g. following bariatric surgery) or in patients taking LT_4 during breakfast [66]. Due to its 28% ethanol content, it is not recommended during pregnancy and breastfeeding or in children and high-risk patients [66]. For patients unable to take oral medications, intravenous administration could be an alternative, with a conversion factor of 75% with respect to the oral dose. LT_4 absorption with food was calculated as 64% compared with 80% in the fasting state [52].

The different pharmacological properties are summarised in Table **1**. Briefly, although patients with NS show specific thyroid hormone profile changes, to the best of our knowledge no prospective studies have assessed which for-

Table 1. Pharmacological properties of different levothyroxine preparations.

	Half-life (h)	Main Site of Metabolism	Main Contraindications	Possible Advantages	Possible Dosage (µg)
Tablets	~ 190	80% peripheral deiodination 20% hepatic metabolism	- Hypersensitivity - Adrenal insufficiency - Hypopituitarism - Thyrotoxicosis		25 50 75 100 125 150 175 200
Gelatin capsules	~ 190	80% peripheral deiodination 20% hepatic metabolism	- Hypersensitivity - Adrenal insufficiency - Hypopituitarism - Thyrotoxicosis	Better absorption during consumption with coffee or PPIs	13 25 50 75 88 100 112 125 137 150 175 200
Liquid formulations	~ 190	80% peripheral deiodination 20% hepatic metabolism	- Hypersensitivity - Adrenal insufficiency - Hypopituitarism - Thyrotoxicosis - Pregnancy/ breastfeeding - Children - High-risk patients	Better absorption in case of malabsorption or in patients taking therapy during breakfast	25 50 75 100

mulation should be preferred to reach euthyroid status as quickly as possible. The only available recommendations originate from a handful of case reports and cannot be considered as reliable.

CONCLUSIONS

The increased prevalence of hypothyroidism and subclinical hypothyroidism in patients with proteinuria is now well known. However, the pathophysiological mechanisms underlying this condition are not completely understood. It is still unclear if hypothyroidism plays a key role in the course of kidney disease or is an innocent bystander. What does seem to be clear is the worse quality of life and poor prognosis of NS patients with hypothyroidism. Thyroid function in patients with NS should thus be assessed as soon as possible, in order to treat this potential complication. Euthyroidism can now be restored by simple and versatile pharmacological treatment, tailored to the patient. Further studies are needed to establish the prevalence and diagnostic challenges of hypothyroidism in the course of NS, to find reliable new thyroid function biomarkers in kidney proteinuric disease and to establish the best replacement therapy.

LIST OF ABBREVIATIONS

DIT	=	Di-iodinated tyrosine
FT_3	=	Free T_3
FT_4	=	Free T_4
LT_4	=	Levothyroxine
MIT	=	Mono-iodinated tyrosine
NS	=	Nephrotic syndrome
T_3	=	Tri-iodothyronine
T_4	=	Thyroxine
TBG	=	Thyroxine-binding globulin
TSH	=	Thyroid-stimulating hormone

CONFLICT OF INTEREST

There are no known conflicts of interest associated with this publication and there has been no financial support for this work.

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