Article / Review

Thyroid Gland and Chronic Kidney Disease in Children

I.A.Karimdzhanov[1] , M.B.Rahmonberdiyeva[1]

Correspondence author: Ilhamdzhan A. Karimdzhanov, Professor, Head of the Department of Children's Diseases in Family Medicine, Tashkent State Medical University, 2 Farobiy St., Tashkent 100109, Uzbekistan.

e-mail: ilkhamdjan@gmail.com.

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1. Tashkent State Medical University, Tashkent, Uzbekistan.

Correspondence: *Tashkent State Medical University, Uzbekistan, 100109, Tashkent, Farobi 2 Street.*

Abstract.

Introduction. Chronic kidney disease in children is accompanied by pronounced metabolic, hormonal, and inflammatory disturbances, among which alterations in thyroid status occupy an important place. As renal function declines, peripheral thyroid hormone metabolism becomes impaired, iodine clearance decreases, chronic inflammation intensifies, and the likelihood of developing a biochemical profile consistent with low T3 syndrome increases. **Aim.** To summarize current evidence on thyroid dysfunction in children with chronic kidney disease and to analyze the main pathogenetic mechanisms, laboratory abnormalities, and clinical significance of thyroid status alterations in this patient population. **Materials and methods.** This study was conducted as a narrative literature review. Recent publications on chronic kidney disease in children, thyroid profile abnormalities associated with reduced renal function, the pathogenetic mechanisms of low T3 syndrome, and the clinical significance of hormonal disturbances in this patient population were reviewed and analyzed. **Results and discussion.** Thyroid dysfunction in children with chronic kidney disease does not always reflect primary thyroid pathology, as it often develops secondary to uremic intoxication, impaired deiodinase activity, chronic inflammation with activation of proinflammatory cytokines, protein-energy deficiency, and metabolic disturbances. The most common hormonal abnormality is low T3 syndrome, which should be regarded as one of the markers of systemic metabolic maladaptation in chronic kidney disease. In childhood, these changes are of particular clinical importance because they may be associated with growth retardation, impaired nutritional status, abnormalities of bone metabolism, and reduced adaptive capacity. **Conclusion.** Thyroid dysfunction in children with chronic kidney disease is a clinically significant manifestation of systemic disorders and requires comprehensive assessment during follow-up, especially in patients with growth retardation, malnutrition, and a marked decline in renal function.

Key words: children, chronic kidney disease, thyroid dysfunction, low T3 syndrome, hypothyroidism, pediatric nephrology.

Introduction. Chronic kidney disease (CKD) in children is associated with substantial metabolic, hormonal, inflammatory, hemodynamic, and cardiovascular disturbances, among which alterations in thyroid status occupy an important place [1,4-7,16,17]. As renal function declines, the conditions necessary for normal peripheral thyroid hormone metabolism become progressively impaired. Iodine clearance decreases, chronic inflammation intensifies, and the likelihood of developing a biochemical profile consistent with low T3 syndrome increases. Several studies have also reported changes in free thyroxine (free T4) and thyroid-stimulating hormone (TSH) levels, while some patients demonstrate features of subclinical hypothyroidism.

Importantly, thyroid dysfunction in children with CKD does not necessarily indicate primary thyroid disease. In many cases, it develops secondary to uremic intoxication, impaired deiodinase activity, chronic inflammation with activation of proinflammatory cytokines, protein-energy wasting, and broader metabolic disturbances. In childhood, these abnormalities are of particular clinical relevance because they may contribute to growth retardation, impaired nutritional status, abnormalities of bone metabolism, and reduced adaptive capacity. This review summarizes current evidence on the mechanisms underlying thyroid dysfunction in children with CKD and discusses the major laboratory patterns and their clinical implications.

Aim of the review. To summarize current evidence on thyroid dysfunction in children with chronic kidney disease, with particular emphasis on pathogenetic mechanisms, laboratory abnormalities, and clinical significance.

Materials and methods. This study was conducted as a narrative literature review. Recent publications addressing CKD in children, changes in thyroid profile associated

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with reduced renal function, the pathogenetic basis of low T3 syndrome, and the clinical significance of hormonal disturbances in this patient population were reviewed and analyzed.

Results and discussion

Physiological relationship between the kidneys and the thyroid gland

Current evidence suggests that thyroid dysfunction in children with CKD develops in a characteristic and multifactorial manner. As renal insufficiency progresses, metabolic disturbances, chronic inflammation, nutritional impairment, abnormalities of protein metabolism, and disruption of mineral homeostasis become more pronounced, creating conditions for altered synthesis, peripheral conversion, transport, and tissue action of thyroid hormones [1,2,4-7]. Accordingly, thyroid abnormalities in children with CKD should be regarded not merely as laboratory manifestations of chronic somatic disease, but also as clinically meaningful components of broader systemic maladaptation [2-4,7].

The close physiological interplay between the kidneys and the thyroid gland helps explain the high frequency of thyroid abnormalities in CKD. The kidneys contribute to iodine excretion, maintenance of water-electrolyte balance, protein homeostasis, and preservation of the internal environment required for normal thyroid hormone metabolism [1,2,8,11]. Because a substantial proportion of iodine is excreted by the kidneys, declining glomerular filtration may lead to altered iodine clearance and redistribution within the body. At the same time, thyroid hormones influence renal blood flow, systemic hemodynamics, glomerular filtration rate, and tubular transport [2,8,11]. This relationship is particularly relevant in pediatric nephrology, where CKD is accompanied by systemic hemodynamic and cardiovascular disturbances reflecting the multisystem nature of renal disease [16,17]. Thus, impaired renal function may result in secondary alterations in thyroid status, whereas thyroid dysfunction may further aggravate pre-existing metabolic and hemodynamic disturbances [2,8-11].

Pathogenetic mechanisms of thyroid dysfunction

One of the principal mechanisms underlying thyroid dysfunction in CKD is impaired peripheral thyroid hormone metabolism. A central role in this process is played by deiodinases, which convert thyroxine (T4) into biologically active triiodothyronine (T3) or into inactive metabolites [2,8,11]. In CKD, deiodinase activity may decrease, resulting in reduced T3 production in peripheral tissues. At the same time, reverse T3 generation may increase, reflecting a shift in hormone metabolism toward metabolic adaptation in the setting of chronic disease [2,8,11]. These changes are especially important in growing children, since T3 is essential for tissue respiration, energy metabolism, growth, and the maturation of organs and systems [4,12,13].

Disturbances in peripheral thyroid hormone metabolism are closely linked to uremic intoxication. As renal function deteriorates, metabolites accumulate in the circulation and exert adverse effects on enzymatic systems, protein metabolism, and cellular sensitivity to hormones [2,8-11]. These factors may alter peripheral thyroid hormone conversion, impair hormone transport, and intensify catabolic processes. Several studies have shown that the degree of T3 reduction often correlates with the severity of renal dysfunction, suggesting that low T3 syndrome may reflect the depth of systemic metabolic maladaptation [3,8-11].

Chronic inflammation also contributes substantially to the pathogenesis of thyroid dysfunction in children with CKD. Even in the absence of overt clinical inflammatory manifestations, these patients often demonstrate persistent activation of immune-inflammatory pathways. Proinflammatory cytokines, particularly interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-alpha), play a pivotal role in this process [14,15]. These mediators reduce deiodinase activity, impair peripheral conversion of T4 to biologically active T3, alter tissue responsiveness to thyroid hormones, and promote catabolic processes [14,15]. IL-6 is considered one of the most important mediators associated with reduced T3 levels in chronic systemic disease [14,15]. TNF-alpha may further aggravate metabolic maladaptation and additionally limit the formation of active T3 in peripheral tissues [14,15]. Consequently, reduced T3 in CKD should be viewed not only as an endocrine abnormality but also as a reflection of systemic inflammatory activity [14,15].

Nutritional impairment and protein-energy deficiency are likewise considered key contributors to thyroid abnormalities in children with CKD. Long-standing kidney disease is often accompanied by loss of appetite, dietary restriction, impaired nutrient absorption, and progressive protein deficiency [4-7,12]. Under these conditions, synthesis of transport proteins decreases, thyroid hormone binding to plasma proteins changes, tissue hormone availability is reduced, and catabolism becomes more pronounced [2,8,10,11]. In children, unlike adults, these disturbances are especially detrimental because they occur during

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periods of active growth and high energy demand [4,12,13]. As a result, thyroid dysfunction in CKD may be closely related not only to the stage of renal insufficiency but also to the severity of nutritional derangement [4,7,12].

Metabolic acidosis, which commonly accompanies CKD progression, is another relevant factor. Disturbances in acid-base balance may affect enzymatic reactions, transport processes, and cellular sensitivity to hormones [1,2,8]. In the setting of acidosis, the overall metabolic profile deteriorates and protein catabolism intensifies, creating additional conditions for impaired thyroid hormone metabolism [4,7,12]. Although the role of metabolic acidosis as an independent mechanism of thyroid dysfunction has not been fully elucidated, its contribution to the adverse metabolic environment of CKD appears substantial [1,2].

Low T3 syndrome and laboratory abnormalities

The most consistently reported thyroid abnormality in children with CKD is low T3 syndrome [2,3,8-11]. This condition is characterized by reduced free or total triiodothyronine levels in the presence of less pronounced, unstable, or even absent changes in TSH and free T4 [3,8-11]. Correct interpretation of this pattern is essential in clinical practice, since it does not always indicate true primary hypothyroidism [2,8,11]. In many cases, low T3 syndrome reflects an adaptive or maladaptive response to prolonged chronic disease, inflammation, uremic intoxication, and nutritional disturbances [2,8-11]. However, when renal dysfunction is severe and prolonged, it may acquire independent clinical significance as a marker of overall disease burden [3,9-11].

Interpretation of low T3 syndrome is particularly important in pediatric patients because thyroid hormones are essential for linear growth, bone maturation, energy metabolism, and overall physical development [4,12,13]. Whereas in adults reduced T3 is often regarded primarily as a marker of systemic illness severity, in children even a moderate but persistent decline in biologically active hormone may have broader developmental consequences [3,4,12,13]. Low T3 syndrome in pediatric CKD should therefore not be considered a minor laboratory abnormality. Its detection requires careful correlation with the patient's clinical condition, growth velocity, nutritional status, and degree of renal impairment [3,4,7,12].

Alterations in TSH and free T4 in children with CKD have been described less consistently. In some studies, TSH and free T4 remained within reference ranges despite reduced T3 levels [3,8,11]. Other reports described subclinical hypothyroidism, particularly in children with markedly reduced glomerular filtration rate, prolonged disease duration, and pronounced metabolic abnormalities [3,9,10]. This heterogeneity may reflect differences in study populations, age, CKD stage, disease duration, underlying renal pathology, and criteria used for hormonal assessment [3,5-7]. In addition, laboratory findings may be influenced by protein status, concomitant treatment, and interlaboratory differences in hormone measurement methods [2,3,8].

It should also be emphasized that thyroid hormone abnormalities in CKD do not always conform to the classic patterns of primary thyroid disease. Therefore, automatic interpretation of any decline in T3 or fluctuation in TSH as true hypothyroidism may be clinically misleading [2,3,8,11]. In such situations, a comprehensive approach is required, incorporating the clinical picture, anthropometric data, CKD stage, presence of inflammation, nutritional deficiency, and laboratory dynamics [1,3-7]. This is especially important in pediatrics, where both overdiagnosis and underrecognition of thyroid abnormalities may influence management and follow-up strategy [3-7].

Clinical significance of thyroid dysfunction in children

The clinical importance of thyroid dysfunction in children with CKD is primarily determined by its possible association with growth retardation. CKD itself is one of the leading causes of impaired physical development in pediatric patients [4-7,12,13]. When thyroid abnormalities, particularly reduced T3, occur in this context, they may further restrict linear growth, impair bone remodeling, and worsen energy deficiency [4,12,13]. Several studies have noted that children with more pronounced thyroid abnormalities tend to have poorer anthropometric indices and more severe nutritional disturbances [3,4,12]. Although causal relationships cannot always be established with certainty, the association between thyroid dysfunction and unfavorable physical development is clinically important [4,12,13].

The relationship between thyroid status and bone metabolism is also of considerable interest. Thyroid hormones are involved in the regulation of bone growth and maturation, while children with CKD commonly develop disturbances of mineral metabolism [1,4-7]. Under these conditions, thyroid dysfunction may further affect bone formation and aggravate skeletal growth impairment [4,12,13]. Although direct pediatric studies assessing

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this relationship remain limited, the pathogenetic rationale is strong.

Another important issue is the possible role of thyroid dysfunction as a marker of CKD severity. In several studies, reduced T3 levels were associated with more advanced renal impairment, greater metabolic instability, and poorer overall clinical status [3,8-11]. This suggests that the thyroid profile may serve not only as an indicator of endocrine status but also as an additional marker of systemic maladaptation in chronic kidney disease [2,8,11]. However, more targeted pediatric studies are needed before the prognostic significance of thyroid parameters in children with CKD can be defined more precisely [3-7].

From a practical perspective, assessment of thyroid status in children with CKD appears especially justified in high-risk groups. These include patients with markedly reduced estimated glomerular filtration rate, growth retardation, malnutrition, signs of chronic inflammation, and prolonged disease duration [1,3-7,12]. The most informative parameters for initial assessment are TSH, free T3, and free T4 [3,8-10]. When appropriate, hormonal findings should be interpreted alongside clinical and nephrological parameters. Such an approach helps avoid both underestimation and overinterpretation of thyroid abnormalities [1-3,8].

Therapeutic management of thyroid abnormalities in children with CKD remains a separate and challenging issue. Not all cases of low T3 syndrome require immediate hormonal correction, since in some patients this pattern reflects a secondary metabolic response to severe chronic disease rather than true primary thyroid insufficiency [2,8,11]. At the same time, when persistent abnormalities in TSH and free T4, clinical signs of hypothyroidism, marked growth retardation, and supportive findings on further evaluation are present, treatment decisions should be individualized. This further underscores that interpretation of thyroid status in pediatric CKD should rely on a clinical-pathogenetic rather than purely laboratory-based approach [3,4,12].

Limitations of available evidence

When interpreting the available literature, several limitations should be taken into account. First, the number of studies specifically focused on pediatric populations is considerably smaller than the number of studies in adults [3-7]. Second, many studies include relatively small cohorts of children differing in age, CKD stage, underlying diagnoses, and laboratory methods [3,5-7,9,10]. Third, some conclusions regarding the pathogenesis of thyroid dysfunction in children are extrapolated from adult data, which is not always fully appropriate given the specific characteristics of childhood [2,8,11]. In addition, different studies use varying criteria to define low T3 syndrome and subclinical hypothyroidism, which complicates direct comparison of results [3,8-10].

Despite these limitations, the currently available evidence supports several important conclusions. First, thyroid dysfunction in children with CKD is relatively common and multifactorial in origin [2,3,8-11]. Second, the most typical laboratory pattern is low T3 syndrome, associated with impaired peripheral hormone metabolism, chronic inflammation, uremic intoxication, and nutritional disturbances [2,8,11,14,15]. Third, thyroid abnormalities in pediatric CKD have not only biochemical but also clinical significance, as they may be linked to growth retardation, disturbed bone metabolism, and generalized metabolic maladaptation [4,12,13]. Finally, assessment of thyroid profile in this patient population is clinically relevant as part of comprehensive follow-up and warrants further investigation in appropriately designed pediatric studies [3-7].

Conclusion. Thyroid dysfunction in children with chronic kidney disease is a characteristic and clinically significant manifestation of the systemic disturbances accompanying progression of renal disease. Alterations in thyroid status arise through a complex interaction of impaired peripheral hormone metabolism, uremic intoxication, chronic inflammation involving proinflammatory cytokines, and metabolic as well as nutritional disturbances. Therefore, thyroid abnormalities should be interpreted not as isolated endocrine deviations, but as components of the broader pathogenetic changes occurring in the child's body during chronic illness.

The most typical hormonal abnormality in pediatric CKD is low T3 syndrome, which may reflect both an adaptive response to prolonged systemic illness and progressive metabolic maladaptation as renal function worsens. In childhood, these abnormalities are especially important because thyroid hormones are closely linked to growth, energy balance, bone maturation, and nutritional status. Reduced T3, fluctuations in TSH, and changes in free T4 in children with CKD should therefore not be dismissed as incidental laboratory findings.

From a practical standpoint, evaluation of thyroid profile in children with CKD is clinically important as part of comprehensive follow-up, particularly in patients with growth

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retardation, malnutrition, chronic inflammation, and markedly reduced glomerular filtration rate. Further pediatric studies are needed to clarify the diagnostic and prognostic significance of thyroid abnormalities and to develop evidence-based monitoring strategies for children with chronic kidney disease.

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About the authors

Ilkhamdzhan A.Karimdzhanov, D.Sc. (Med.), Professor, ORCID ID: 0000-0002-9356-4870, e-mail: ilkhamdjan@gmail.com; Professor, Head of the Department of Children's Diseases in Family Medicine, Tashkent State Medical University, 2 Farobiy St., Tashkent 100109, Uzbekistan.

Matluba B.Rahmonberdiyeva, ORCID ID: 0009-0003-2992-4848 e-mail: mrahmonberdiyeva@gmail.com; Assistant, Department of Children's Diseases in Family Medicine, Tashkent State Medical University, 2 Farobiy St., Tashkent 100109, Uzbekistan. Tel.: +998909212588. (Corresponding author).

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