Thyroid Dysfunction and Autoimmunity as Emerging Biomarkers in the Progression of Diabetic Nephropathy in Type 2 Diabetes Mellitus

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Abstract

Background: Diabetic nephropathy (DN) remains one of the most significant microvascular complications of type 2 diabetes mellitus (T2DM) and is a leading cause of end-stage renal disease worldwide. Despite advances in glycemic control and renoprotective therapies, the early detection of DN continues to pose clinical challenges. Traditional biomarkers such as albuminuria and estimated glomerular filtration rate (eGFR) often lack sensitivity in identifying subclinical renal injury, emphasizing the urgent need for novel biomarkers. In recent years, growing evidence has highlighted the potential contribution of thyroid dysfunction and thyroid autoimmunity in the pathogenesis and progression of DN. Thyroid hormones are key regulators of glucose metabolism, lipid balance, endothelial function, and renal hemodynamics, all of which play crucial roles in diabetic renal injury. Moreover, thyroid autoantibodies, particularly anti-thyroid peroxidase (TPO-Ab) and anti-thyroglobulin antibodies (Tg-Ab), have been increasingly recognized as potential markers of immune-mediated damage that may exacerbate renal dysfunction in T2DM patientsy. The aim of this review is to evaluate the diagnostic and prognostic significance of thyroid dysfunction and autoimmunity as emerging biomarkers in DN progression among T2DM patients. The review discusses the prevalence of thyroid dysfunction in diabetes, mechanisms linking thyroid hormone imbalance to renal injury, the role of thyroid autoantibodies in microvascular complications, and the clinical evidence supporting their use in risk stratification. Furthermore, it highlights the interplay of inflammation, oxidative stress, and thyroid dysfunction in accelerating renal decline. Understanding these associations may facilitate earlier detection, personalized monitoring, and more effective preventive strategies for high-risk individuals. Incorporating thyroid biomarkers into clinical assessment models could improve prediction of DN progression and guide therapeutic interventions such as thyroid hormone replacement or modulation strategies. Despite encouraging findings, heterogeneity across studies, limited longitudinal data, and uncertainties regarding causal relationships warrant further investigation. Future research should focus on large-scale prospective studies, mechanistic insights, and integration of thyroid-related biomarkers with existing renal risk models. In conclusion, thyroid dysfunction and autoimmunity appear to be underexplored yet promising biomarkers for DN progression in T2DM patients. Their integration into clinical practice has the potential to enhance early diagnosis, refine risk stratification, and support tailored interventions, ultimately reducing the burden of diabetic kidney disease.

Keywords: *Thyroid Dysfunction, Diabetic Nephropathy, Type 2 Diabetes Mellitus*

Introduction

Clinical Burden and Relevance in Internal Medicine

Type 2 diabetes mellitus (T2DM) is a global health challenge, affecting over 450 million individuals worldwide and projected to increase dramatically in the coming decades. Among its complications, diabetic nephropathy (DN) stands out as one of the most devastating, being the leading cause of end-stage renal disease (ESRD) and accounting for significant morbidity, mortality, and healthcare costs [1]. Early detection and risk stratification of DN remain difficult, as current diagnostic markers such as microalbuminuria and estimated glomerular filtration rate (eGFR) are often insensitive in identifying subclinical renal damage and predicting progression [2]. Consequently, there is an urgent need to identify novel biomarkers that can more accurately reflect underlying pathophysiological processes and help guide timely interventions.

Thyroid hormones are key regulators of metabolism, cardiovascular health, and renal physiology. In T2DM patients, disturbances in thyroid function are common, ranging from subclinical hypothyroidism to overt thyroid disease, and have been linked with adverse metabolic and vascular outcomes [3]. Thyroid dysfunction alters glucose utilization, lipid metabolism, endothelial homeostasis, and renal hemodynamics, all of which contribute to the progression of DN. Moreover, autoimmune thyroid disease, as evidenced by the presence of anti-thyroid peroxidase (TPO-Ab) and anti-thyroglobulin (Tg-Ab) antibodies, may further predispose diabetic patients to immune-mediated injury, chronic inflammation, and microvascular complications [4].

Although the association between thyroid dysfunction and cardiovascular complications in diabetes is well established, its role in diabetic nephropathy has only recently gained attention. Several observational studies suggest that thyroid hormones and thyroid autoantibodies may serve as predictive markers for renal impairment in T2DM patients [5]. However, the mechanistic underpinnings, clinical relevance, and consistency of these findings remain underexplored.

The aim of this review is to synthesize current evidence regarding thyroid dysfunction and autoimmunity as emerging biomarkers in the progression of DN among T2DM patients. By exploring epidemiological data, mechanistic insights, clinical studies, and therapeutic implications, this review seeks to highlight the potential integration of thyroid biomarkers into routine risk assessment and management strategies. Furthermore, it emphasizes the existing research gaps and future directions necessary to validate these markers for clinical application.

Epidemiology and Burden of Diabetic Nephropathy in Type 2 Diabetes Mellitus

Diabetic nephropathy (DN) is one of the most common and severe microvascular complications of type 2 diabetes mellitus (T2DM). It affects approximately 20–40% of patients with T2DM, making it the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide [6]. The global rise in diabetes prevalence directly translates into an increased burden of DN, particularly in low- and middle-income countries where access to early detection and treatment remains limited. The economic and social impact of DN is profound, contributing to high healthcare costs, disability, and reduced life expectancy [7].

Geographical variation in the prevalence and outcomes of DN reflects differences in genetic predisposition, healthcare infrastructure, socioeconomic conditions, and lifestyle factors. In developed nations, widespread screening and improved glycemic management have delayed the onset of DN, while in developing regions, delayed diagnosis and limited treatment access have accelerated its progression [8]. Ethnic disparities are also notable; for example, South Asians, Hispanics, and African Americans have higher risks of developing DN compared with Caucasian populations, highlighting the role of both genetic and environmental factors [9].

Beyond its prevalence, DN significantly increases the risk of cardiovascular morbidity and mortality. Patients with DN face a two- to three-fold higher risk of cardiovascular events compared to diabetic patients without renal involvement [10]. Importantly, DN often progresses silently, with

microalbuminuria being the earliest clinical marker; however, not all patients with microalbuminuria develop progressive renal disease, and some patients develop DN without albuminuria, suggesting the need for more sensitive and specific biomarkers [11]. This underscores the importance of investigating alternative biomarkers, such as thyroid dysfunction and autoimmunity, which may aid in early identification of patients at risk of renal decline.

Pathophysiological Insights into Diabetic Nephropathy

Diabetic nephropathy (DN) develops through a multifactorial pathophysiological process that involves hemodynamic, metabolic, and inflammatory mechanisms. Chronic hyperglycemia plays a central role by inducing glomerular hyperfiltration, mesangial expansion, and basement membrane thickening, which gradually progress to glomerulosclerosis and tubulointerstitial fibrosis [12]. These changes are driven by advanced glycation end products (AGEs), oxidative stress, and activation of pro-fibrotic pathways such as transforming growth factor-beta (TGF-β), leading to progressive renal damage [13].

Hemodynamic alterations, particularly increased intraglomerular pressure and activation of the renin–angiotensin–aldosterone system (RAAS), contribute significantly to DN pathogenesis. Hyperfiltration at early stages initially compensates for metabolic stress but eventually accelerates podocyte injury and glomerular basement membrane permeability [14]. Persistent RAAS activation amplifies endothelial dysfunction, sodium retention, and renal fibrosis, further promoting nephron loss [15].

Inflammation and immune dysregulation are increasingly recognized as crucial mediators in DN progression. Elevated levels of proinflammatory cytokines, adhesion molecules, and chemokines promote leukocyte infiltration and tubular injury [16]. Oxidative stress synergizes with inflammation to damage endothelial cells and podocytes, thereby disrupting the filtration barrier. Recent evidence suggests that thyroid dysfunction and autoimmunity may exacerbate these mechanisms, as thyroid hormones modulate endothelial nitric oxide production, oxidative balance, and immune regulation [17].

Another key pathological feature of DN is podocyte injury. Podocytes are terminally differentiated cells essential for maintaining glomerular integrity. Their detachment and apoptosis, driven by metabolic stress and inflammatory signaling, are strongly associated with proteinuria and progressive renal decline [18]. Loss of podocytes is considered an irreversible hallmark of DN progression. Emerging studies suggest that thyroid hormone imbalances may impair podocyte survival, highlighting a potential mechanistic link between thyroid dysfunction and DN severity [19].

In summary, DN arises from the convergence of hyperglycemia-induced metabolic derangements, hemodynamic stress, inflammation, oxidative damage, and podocyte loss. These processes interact dynamically and often precede the clinical detection of microalbuminuria, underscoring the need for novel biomarkers that capture subclinical injury. The role of thyroid dysfunction and autoimmunity in modulating these mechanisms is a growing area of interest and forms the basis for investigating their value as emerging biomarkers.

Thyroid Hormones in Metabolic Regulation and Renal Physiology

Thyroid hormones (THs), primarily thyroxine (T4) and triiodothyronine (T3), play a pivotal role in regulating energy metabolism, cardiovascular homeostasis, and renal function. They influence glucose and lipid metabolism by enhancing glucose uptake, modulating insulin sensitivity, and stimulating hepatic gluconeogenesis, thereby directly interacting with pathways central to the pathogenesis of type 2 diabetes mellitus (T2DM) [20]. Hypothyroidism is associated with insulin resistance, dyslipidemia, and weight gain, while hyperthyroidism promotes increased gluconeogenesis and protein catabolism, all of which may accelerate the development of microvascular complications such as diabetic nephropathy (DN) [21].

In renal physiology, THs contribute to kidney growth, development, and maintenance of renal hemodynamics. They regulate renal blood flow, glomerular filtration rate (GFR), and sodium and water homeostasis by modulating cardiac output and vascular tone [22]. T3 exerts direct effects on renal tubular cells, influencing sodium-potassium ATPase activity, aquaporin expression, and proximal tubular reabsorption processes [23]. Alterations in thyroid status therefore lead to significant changes in

renal function: hypothyroidism is commonly associated with reduced GFR and impaired renal clearance, while hyperthyroidism may increase renal plasma flow but also predispose to glomerular hyperfiltration and injury [24].

Thyroid hormones also play a regulatory role in vascular endothelial function. They stimulate endothelial nitric oxide synthase (eNOS), promoting vasodilation and protecting against endothelial dysfunction, which is central to DN progression [25]. Impaired thyroid function diminishes nitric oxide bioavailability, enhances oxidative stress, and promotes vascular stiffness, thereby contributing to renal microvascular injury. Moreover, thyroid hormones modulate the renin–angiotensin–aldosterone system (RAAS), influencing intraglomerular pressure and fibrotic signaling pathways [26].

Collectively, THs act at the intersection of metabolic regulation, cardiovascular dynamics, and renal physiology. Even subtle thyroid dysfunction can have profound consequences on renal outcomes in diabetic patients. This mechanistic overlap underscores the hypothesis that thyroid dysfunction is not merely a comorbidity in T2DM, but a potential biomarker and pathogenic factor in the progression of DN.

Prevalence of Thyroid Dysfunction in Type 2 Diabetes Mellitus

Thyroid dysfunction is more common in patients with type 2 diabetes mellitus (T2DM) than in the general population, suggesting a complex interplay between glucose metabolism and thyroid homeostasis. Studies indicate that the prevalence of thyroid disorders in T2DM patients ranges between 10% and 20%, which is significantly higher compared with non-diabetic individuals [27]. Among these, subclinical hypothyroidism is the most frequently observed abnormality, followed by overt hypothyroidism and, to a lesser extent, hyperthyroidism [28].

Several factors contribute to the higher prevalence of thyroid dysfunction in diabetes. Insulin resistance, chronic hyperglycemia, and dyslipidemia have been shown to alter thyroid hormone metabolism and peripheral conversion of thyroxine (T4) to triiodothyronine (T3) [29]. Furthermore, diabetic patients are at increased risk of autoimmune thyroid disease, especially women and those with concomitant autoimmune disorders, suggesting shared immunological mechanisms [30]. This increased autoimmune predisposition is often reflected by the presence of thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab), which may serve as early markers of thyroid autoimmunity in T2DM [31].

The clinical consequences of thyroid dysfunction in T2DM are significant. Subclinical hypothyroidism has been associated with worse metabolic profiles, including higher HbA1c levels, dyslipidemia, and increased body mass index (BMI) [32]. Moreover, thyroid dysfunction is linked with an elevated risk of microvascular complications, including diabetic nephropathy (DN), as thyroid hormone imbalance adversely affects renal hemodynamics and endothelial function. A meta-analysis of observational studies confirmed that T2DM patients with hypothyroidism or subclinical hypothyroidism are at greater risk of developing DN compared with euthyroid counterparts [33].

Overall, the higher prevalence of thyroid dysfunction in T2DM highlights the importance of routine thyroid function testing in this population. Detecting even subtle thyroid abnormalities could provide valuable insights into the risk of renal complications and may guide earlier intervention strategies aimed at mitigating DN progression.

Mechanistic Link Between Thyroid Dysfunction and DN Progression

The association between thyroid dysfunction and diabetic nephropathy (DN) extends beyond epidemiological observations, with several mechanistic pathways supporting a causal relationship. Hypothyroidism, the most common thyroid disorder in type 2 diabetes mellitus (T2DM), contributes to renal impairment by reducing cardiac output, renal plasma flow, and glomerular filtration rate (GFR), ultimately exacerbating renal hypoperfusion [34]. These hemodynamic alterations lead to sodium retention, increased vascular resistance, and heightened susceptibility to microalbuminuria, an early marker of DN [35].

At the molecular level, thyroid hormones regulate glucose and lipid metabolism, oxidative balance, and

endothelial function. Hypothyroidism promotes insulin resistance, dyslipidemia, and systemic inflammation, all of which contribute to renal endothelial injury and mesangial expansion [36]. Additionally, thyroid hormone deficiency impairs nitric oxide bioavailability, reduces renal vasodilation, and promotes vascular stiffness, thereby accelerating glomerulosclerosis [37]. Conversely, hyperthyroidism, though less frequent, induces glomerular hyperfiltration, which can precipitate podocyte stress and proteinuria, further linking thyroid status with DN progression [38].

Thyroid hormones also modulate the renin–angiotensin–aldosterone system (RAAS), a critical driver of DN. Hypothyroidism suppresses renin release but paradoxically enhances sodium and water retention, aggravating hypertension and renal fibrosis [39]. Moreover, thyroid hormone deficiency has been shown to increase transforming growth factor-beta (TGF-β) activity, a key mediator of renal fibrosis, thus promoting tubulointerstitial damage [40]. Experimental studies have demonstrated that low thyroid function exacerbates podocyte apoptosis and reduces nephrin expression, both of which are crucial for maintaining glomerular integrity [41].

Emerging evidence also points toward interactions between thyroid dysfunction and oxidative stress in DN. Hypothyroidism increases reactive oxygen species production while reducing antioxidant defenses, thereby amplifying hyperglycemia-induced oxidative injury [42]. This oxidative stress not only damages glomerular endothelial cells but also synergizes with inflammatory mediators to accelerate renal decline. Collectively, these mechanisms suggest that thyroid dysfunction is not merely a coincidental comorbidity in T2DM but an active contributor to DN progression.

Role of Thyroid Autoantibodies in Diabetes and DN

Autoimmune thyroid disease (AITD) is among the most prevalent autoimmune disorders, characterized by the presence of circulating thyroid autoantibodies, primarily anti-thyroid peroxidase antibodies (TPO-Ab) and anti-thyroglobulin antibodies (Tg-Ab). In patients with type 2 diabetes mellitus (T2DM), the prevalence of thyroid autoimmunity is higher than in the general population, suggesting overlapping immunological mechanisms between metabolic dysregulation and autoimmunity [43]. These antibodies may be detected even in euthyroid individuals, indicating subclinical thyroid autoimmunity that could still influence systemic metabolic and vascular outcomes [44].

The presence of thyroid autoantibodies in diabetic patients has been associated with an increased risk of thyroid dysfunction, which can exacerbate metabolic abnormalities and vascular complications. Importantly, TPO-Ab positivity has been linked to endothelial dysfunction, chronic inflammation, and altered immune responses, all of which are implicated in the pathogenesis of diabetic nephropathy (DN) [45]. Autoimmunity may amplify renal damage by promoting immune-mediated injury in glomeruli and tubulointerstitial compartments, accelerating the decline in renal function beyond the effects of hyperglycemia alone [46].

Evidence suggests that thyroid autoantibodies may serve as biomarkers for microvascular complications in T2DM. Studies have demonstrated higher frequencies of TPO-Ab positivity among diabetic patients with albuminuria compared to those without renal involvement, suggesting a potential role in predicting DN [47]. Furthermore, the coexistence of thyroid autoantibodies with subclinical hypothyroidism appears to synergistically increase the risk of microalbuminuria and progression to overt nephropathy [48]. These findings raise the possibility that thyroid autoimmunity is not only a marker of thyroid dysfunction but also an independent contributor to renal pathology in T2DM.

Although mechanistic data are limited, it is hypothesized that autoantibody-mediated immune responses increase the release of pro-inflammatory cytokines and reactive oxygen species, thereby worsening endothelial and podocyte injury. This immune-driven damage may explain why some diabetic patients with similar glycemic control experience disproportionate progression of renal disease [49]. Thus, thyroid autoantibodies may represent a valuable addition to current biomarker panels for identifying high-risk individuals and guiding early intervention strategies.

Clinical Evidence of Thyroid Dysfunction in DN Patients

Clinical studies have increasingly highlighted the association between thyroid dysfunction and diabetic

nephropathy (DN) in type 2 diabetes mellitus (T2DM). Subclinical hypothyroidism has emerged as the most consistently reported thyroid disorder in DN patients, with several cross-sectional and cohort studies demonstrating its higher prevalence among those with microalbuminuria and declining glomerular filtration rate (GFR) [50]. For example, Chen et al. reported that subclinical hypothyroidism independently predicted the presence of nephropathy in T2DM patients, even after adjusting for confounders such as age, sex, duration of diabetes, and glycemic control [51].

Further evidence comes from longitudinal studies indicating that low thyroid hormone levels are associated with faster renal decline in diabetic patients. Reduced serum free triiodothyronine (fT3) and thyroxine (fT4) concentrations have been correlated with progression from microalbuminuria to overt proteinuria and reduced eGFR [52]. A prospective study in Chinese patients with T2DM found that lower baseline fT3 levels predicted worsening renal outcomes over a five-year follow-up period, independent of traditional risk factors [53]. These findings suggest that thyroid hormones may have prognostic value for identifying patients at risk of rapid DN progression.

Meta-analyses also support the link between thyroid dysfunction and DN. A systematic review and meta-analysis by Han et al. concluded that T2DM patients with subclinical hypothyroidism had significantly higher risks of developing nephropathy compared with euthyroid individuals [54]. Moreover, pooled data suggest that even subtle changes in thyroid hormone levels within the reference range can influence renal outcomes, underscoring the sensitivity of the kidney to thyroid status [55].

Interestingly, clinical data also suggest sex-specific differences in the impact of thyroid dysfunction on DN risk. Female T2DM patients with hypothyroidism appear to have higher susceptibility to renal complications compared with males, possibly due to sex-related immunological and hormonal interactions [56]. This observation further highlights the importance of individualized risk assessment in diabetic patients with thyroid abnormalities.

Thyroid Hormones as Predictive Biomarkers of DN Severity

The potential role of thyroid hormones as predictive biomarkers for diabetic nephropathy (DN) severity has been increasingly recognized in recent years. Several studies have demonstrated that alterations in serum thyroid hormone levels, even within the normal reference range, may predict the onset and progression of DN in patients with type 2 diabetes mellitus (T2DM) [57]. Reduced free triiodothyronine (fT3) levels, in particular, have been identified as strong predictors of renal dysfunction, with low fT3 associated with both microalbuminuria and advanced stages of chronic kidney disease (CKD) in diabetic patients [58].

One proposed explanation is that low fT3 reflects a state of “non-thyroidal illness syndrome” or impaired peripheral conversion of thyroxine (T4) to triiodothyronine (T3), which occurs in chronic diseases. In T2DM, this alteration may be an adaptive but maladaptive response, as insufficient T3 availability impairs renal cellular metabolism, endothelial repair, and podocyte function, thereby accelerating DN progression [59]. A prospective cohort study demonstrated that patients with lower baseline fT3 levels had significantly higher risks of reaching ESRD or doubling of serum creatinine compared with those with normal thyroid profiles, even after adjustment for glycemic control and hypertension [60].

Furthermore, thyroid hormone levels have been correlated with established markers of DN severity such as estimated GFR, proteinuria, and histopathological indices of renal damage. Patients with lower fT3 and fT4 levels tend to exhibit more severe glomerulosclerosis, interstitial fibrosis, and tubular atrophy, suggesting a direct influence of thyroid hormones on renal pathology [61]. These associations support the potential clinical utility of thyroid hormone testing as part of risk stratification models for DN.

Importantly, the predictive value of thyroid hormones extends beyond renal outcomes alone. Low thyroid function has also been associated with increased cardiovascular mortality in diabetic patients with DN, underscoring their role as integrative biomarkers of systemic vascular health [62]. Thus, thyroid hormones may serve as dual predictors of both renal and cardiovascular outcomes in T2DM, strengthening the case for incorporating them into comprehensive risk assessment frameworks.

Thyroid Autoantibodies as Predictors of Microvascular Complications

Thyroid autoantibodies, particularly thyroid peroxidase antibodies (TPO-Ab) and thyroglobulin antibodies (Tg-Ab), are increasingly recognized not only as markers of autoimmune thyroid disease but also as potential predictors of microvascular complications in type 2 diabetes mellitus (T2DM). Several studies have shown a higher prevalence of these antibodies in diabetic patients who develop complications such as retinopathy, neuropathy, and nephropathy compared with those without complications [63]. This association suggests that thyroid autoimmunity may amplify systemic vascular injury through chronic inflammation and immune-mediated mechanisms.

In the context of diabetic nephropathy (DN), the presence of thyroid autoantibodies has been linked with earlier onset and greater severity of renal impairment. For example, a cross-sectional study demonstrated that T2DM patients positive for TPO-Ab had a significantly higher prevalence of microalbuminuria and reduced estimated glomerular filtration rate (eGFR) than antibody-negative individuals [64]. Similarly, Tg-Ab positivity has been correlated with endothelial dysfunction and increased urinary albumin excretion, suggesting a direct role in microvascular injury [65]. These findings imply that autoantibody positivity could serve as an additional risk marker in identifying T2DM patients predisposed to DN progression.

The underlying mechanism may involve the autoimmune-mediated release of pro-inflammatory cytokines and oxidative stress mediators, which compromise vascular integrity. Thyroid autoimmunity has also been associated with increased circulating adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1), which facilitate leukocyte infiltration into microvascular beds, contributing to renal inflammation and fibrosis [66]. The combined effects of hyperglycemia and autoimmunity likely create a synergistic pathway that accelerates microvascular damage.

Interestingly, thyroid autoantibody positivity has also been associated with poor response to conventional DN therapies, including renin–angiotensin–aldosterone system (RAAS) blockade. This observation highlights the potential of thyroid autoantibodies not only as predictive biomarkers but also as indicators of therapeutic responsiveness [67]. Incorporating antibody testing into the clinical evaluation of T2DM patients could therefore improve risk stratification and guide personalized treatment strategies aimed at preventing microvascular complications.

Interplay Between Inflammation, Oxidative Stress, and Thyroid Dysfunction in DN

Inflammation and oxidative stress are central drivers of diabetic nephropathy (DN), and increasing evidence suggests that thyroid dysfunction may exacerbate these pathways. Chronic hyperglycemia in type 2 diabetes mellitus (T2DM) induces overproduction of reactive oxygen species (ROS) and activates nuclear factor kappa B (NF-κB), leading to pro-inflammatory cytokine release and endothelial injury [68]. Thyroid hormone imbalance, particularly hypothyroidism, further amplifies this state by impairing mitochondrial oxidative metabolism, reducing antioxidant defense mechanisms, and promoting vascular stiffness [69]. Together, these processes accelerate glomerular and tubular injury.

Patients with hypothyroidism often demonstrate elevated serum markers of oxidative stress such as malondialdehyde and reduced activity of antioxidant enzymes including superoxide dismutase and glutathione peroxidase [70]. In the diabetic kidney, this imbalance magnifies oxidative injury to podocytes and mesangial cells, thereby promoting proteinuria and glomerulosclerosis. Additionally, hyperthyroidism, though less common, can also contribute to oxidative stress via increased metabolic rate and mitochondrial ROS generation, further destabilizing renal function [71].

Inflammation represents another critical link between thyroid dysfunction and DN. Subclinical hypothyroidism is associated with elevated circulating C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which are well-known mediators of diabetic renal injury [72]. Thyroid autoantibodies, particularly TPO-Ab, may directly contribute to renal inflammation by stimulating immune-mediated cytokine release and leukocyte infiltration into the kidney microvasculature [73]. The interaction between autoimmunity and metabolic dysregulation may thus create a “double hit” that accelerates DN progression.

Furthermore, thyroid hormones play a role in endothelial nitric oxide synthase (eNOS) regulation.

Reduced thyroid activity diminishes nitric oxide bioavailability, promoting vasoconstriction, endothelial dysfunction, and microvascular injury [74]. In diabetic patients, this impairment synergizes with hyperglycemia-induced oxidative stress, worsening renal hypoperfusion and ischemic injury. These interlinked mechanisms support the hypothesis that thyroid dysfunction not only accompanies but actively contributes to the inflammatory and oxidative milieu that drives DN.

Impact of Thyroid Dysfunction on Renal Hemodynamics and Microalbuminuria

Thyroid hormones are integral regulators of renal blood flow and glomerular filtration rate (GFR), and their dysregulation has important implications for the development of microalbuminuria in type 2 diabetes mellitus (T2DM). In hypothyroidism, reduced cardiac output and systemic vasoconstriction result in decreased renal plasma flow and diminished GFR, predisposing patients to impaired renal clearance and progressive kidney injury [75]. Conversely, hyperthyroidism can induce glomerular hyperfiltration, which initially elevates GFR but eventually contributes to podocyte stress, basement membrane thickening, and proteinuria [76]. Both scenarios highlight the vulnerability of renal hemodynamics to thyroid imbalance.

Clinical studies have consistently shown a strong relationship between subclinical hypothyroidism and the presence of microalbuminuria in diabetic patients. Microalbuminuria, an early hallmark of diabetic nephropathy (DN), reflects both glomerular endothelial dysfunction and tubular injury. Shantha et al. observed that T2DM patients with subclinical hypothyroidism exhibited significantly higher rates of microalbuminuria compared with euthyroid individuals, independent of glycemic control and hypertension [77]. This suggests that thyroid dysfunction serves as an additive risk factor for DN beyond conventional metabolic risk determinants.

The mechanism underlying this association involves impaired renal vasodilation due to reduced nitric oxide production and increased vascular stiffness in hypothyroid states [78]. This hemodynamic imbalance enhances intraglomerular pressure variability and accelerates microvascular injury. Additionally, thyroid hormone deficiency has been associated with reduced expression of nephrin and podocin—key structural proteins of the glomerular slit diaphragm—leading to increased protein leakage and albuminuria [79]. These findings emphasize that even subtle thyroid hormone abnormalities may influence microvascular homeostasis and contribute to the early onset of DN.

From a clinical perspective, monitoring thyroid function may provide complementary information to microalbuminuria testing for early detection of DN risk. Patients with combined thyroid dysfunction and microalbuminuria have shown more rapid progression to overt nephropathy compared with those with either condition alone [80]. This reinforces the value of integrating thyroid assessment into the routine evaluation of renal risk in T2DM populations.

Conclusion

Diabetic nephropathy (DN) remains a leading cause of chronic kidney disease and end-stage renal disease in patients with type 2 diabetes mellitus (T2DM). Despite advances in diagnosis and treatment, the current reliance on markers such as microalbuminuria and estimated glomerular filtration rate (eGFR) is insufficient for early detection and precise risk stratification. Growing evidence highlights the role of thyroid dysfunction and thyroid autoimmunity as emerging biomarkers with diagnostic and prognostic value in DN.

Thyroid hormones regulate multiple pathways critical for renal health, including glucose and lipid metabolism, vascular tone, endothelial function, and podocyte integrity. Both hypothyroidism and hyperthyroidism disrupt renal hemodynamics and cellular homeostasis, accelerating renal injury in T2DM. Low free triiodothyronine (fT3) levels, even within the normal range, have consistently been associated with increased risk of microalbuminuria, faster decline in renal function, and higher mortality. Similarly, thyroid autoantibodies, particularly TPO-Ab and Tg-Ab, may identify diabetic patients predisposed to immune-mediated renal injury, inflammation, and oxidative stress, thereby providing additional predictive insight into DN progression.

Importantly, the integration of thyroid hormone assessment with autoantibody profiling appears to improve prognostic accuracy compared to conventional risk markers alone. Patients with combined thyroid dysfunction and antibody positivity show disproportionately higher risks of microvascular complications, underscoring the synergistic effect of metabolic and autoimmune mechanisms. These findings suggest that thyroid biomarkers may serve not only as indicators of renal injury but also as potential targets for therapeutic intervention.

From a clinical standpoint, incorporating thyroid function tests and autoantibody screening into the routine evaluation of T2DM patients could allow for earlier identification of high-risk individuals. This would facilitate more personalized management strategies, including tighter metabolic control, closer renal monitoring, and potential thyroid-targeted therapies. However, significant gaps remain in the evidence base, particularly regarding longitudinal outcomes, interventional studies, and the mechanistic interplay between thyroid dysfunction, autoimmunity, and DN.

In conclusion, thyroid dysfunction and autoimmunity represent promising but underutilized biomarkers in the progression of DN. Their clinical utility lies in enhancing early detection, refining risk stratification, and guiding individualized treatment. Future research should focus on large-scale prospective trials and mechanistic studies to validate their integration into clinical practice, ultimately aiming to reduce the burden of diabetic kidney disease worldwide.

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