

## Case Report


# A rare case of Hashimoto's thyroiditis with nephrotic syndrome - A case report

E.A. Ashok Kumar<sup>1\*</sup>, Neelamraju Sai Mounika<sup>2</sup>

<sup>1</sup>Professor, <sup>2</sup>Post Graduate

Department of General Medicine, Malla Reddy Institute of Medical Sciences, Hyderabad, Telangana, India

\*Corresponding author email: [ashokedla@gmail.com](mailto:ashokedla@gmail.com)

	International Archives of Integrated Medicine, Vol. 8, Issue 5, May, 2021.	
	Available online at <a href="http://iaimjournal.com/">http://iaimjournal.com/</a>	
	ISSN: 2394-0026 (P)	ISSN: 2394-0034 (O)
	Received on: 20-04-2021	Accepted on: 27-04-2021
	Source of support: Nil	Conflict of interest: None declared.
<b>How to cite this article:</b> E.A. Ashok Kumar, Neelamraju Sai Mounika. A rare case of Hashimoto's thyroiditis with nephrotic syndrome - A case report. IAIM, 2021; 8(5): 67-75.		

## Abstract

Hashimoto's thyroiditis is generally associated with hypothyroidism. It affects ~2% of the female population and 0.2% of the male population. The evidence of thyroid function and thyroid autoantibody unrelated microproteinuria in almost 50% of patients with Hashimoto's thyroiditis and sometimes heavy proteinuria as in the nephrotic syndrome points to a link of Hashimoto's thyroiditis with renal disease. The most common renal disease observed in Hashimoto's thyroiditis is membranous nephropathy. Different hypotheses have been put forward regarding the relationship between Hashimoto's thyroiditis and glomerulopathies. Glomerular deposition of immunocomplexes of thyroglobulin and autoantibodies as well as the impaired immune tolerance for megalin are the most probable mechanisms. We herewith present a case report of Hashimoto's thyroiditis with Nephrotic Syndrome.

## Key words

Hashimoto's thyroiditis, Nephrotic syndrome.

## Introduction

The interaction between thyroid hormones and kidney is an important factor in the normal functioning of both the organs. Thyroid hormones, on the one hand, play a major role in the early development of kidney structurally and thereafter in the regulation of major glomerular and tubular functions as well as water and

electrolyte balance. Kidneys, on the other hand, are important in the metabolism and elimination of thyroid hormones [1]. A defect in functioning of either organs are expected to have consequences on both the systems. Most Renal diseases are characterized by the presence of proteinuria. Although albumin constitutes the major fraction of protein excreted due to selective nature of proteinuria, many other

important globulins, hormones and hormone binding proteins are also excreted in significant amounts. Urinary loss of thyroxine and thyroid binding globulins (TBG) are one of the important concerns. In early stages no metabolic consequences are expected as levels of free Triiodothyronine (fT3) and free Thyroxine (fT4) remain normal. But prolonged excretions of TBG will reduce levels of free thyroid hormones, which leads to rise in thyroid stimulating hormone (TSH) levels as the thyroid gland starts to over-function [2]. Most of the patients are able to maintain a clinical euthyroid state with these changes, patients with low thyroid reserves can develop overt hypothyroidism. Autoimmunity, which can attack both the organs simultaneously, can also contribute considerably to abnormal functioning of both the organs [3, 4]. Regardless of the cause, simultaneous dysfunction of both the organs can substantially contribute to the patients morbidity. Thus, a thorough knowledge of exact pathophysiology is required to plan an effective treatment protocol in these patients. Although there are a few studies and case reports of hypothyroidism with nephrotic syndrome, substantial data are still lacking to study the thyroid hormone status and its clinical relevance in patients with nephrotic syndrome.

Nephrotic syndrome is one of the best-known presentations of adult kidney disease. It can be caused by a wide range of primary (idiopathic) and secondary glomerular diseases. It is, in fact, an important manifestation of kidney disease [5]. Nephrotic syndrome, characterized mainly by urinary protein loss, also results in urinary losses of binding proteins, such as thyroxine binding globulin (TBG), transthyretin or prealbumin, albumin, and thyroid hormones bound to them. Some researchers think hypothyroidism-associated nephrotic syndrome seems to be related more to the decline in thyroid hormone levels rather than to thyroid autoimmunity [6].

Autoimmune thyroiditis (AIT) is generally associated with hypothyroidism. It affects ~2% of the female population and 0.2% of the male

population. The evidence of thyroid function and thyroid autoantibody - unrelated microproteinuria in almost half of the patients with AIT and sometimes heavy proteinuria as in the nephrotic syndrome point to a link of AIT with renal disease. The most common renal diseases observed in AIT are membranous nephropathy, membranoproliferative, glomerulonephritis, minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, antineutrophil cytoplasmic autoantibody (ANCA) vasculitis, and amyloidosis. Different hypotheses have been proposed regarding the relationship between AIT and glomerulopathies, and several potential mechanisms for this association were also considered. Glomerular deposition of immunocomplexes of thyroglobulin and autoantibodies as well as the impaired immune tolerance for megalin (a thyrotropin-regulated glycoprotein expressed on thyroid cells) are the most probable mechanisms. Cross-reactivity between antigens in the setting of genetic predisposition was considered as a potential mechanism that links the described association between ANCA vasculitis and AIT.

Hashimoto's thyroiditis is the leading form of autoimmune thyroiditis (AIT), which is the most prevalent autoimmune disorder and the most common cause of hypothyroidism, excluding iodine insufficiency. It affects ~2% of the female population and 0.2% of the male population [7]. This condition is well known to be associated with other autoimmune diseases, the most common of which are chronic autoimmune gastritis, vitiligo, rheumatoid arthritis, polymyalgia rheumatica, celiac disease, type 1 diabetes, Sjögren's syndrome, systemic lupus erythematosus (SLE), multiple sclerosis, and sarcoidosis [8]. Also glomerular disease may be related to autoimmune disease with several mechanisms [9].

Glomerular disease related to AIT Glomerular involvement in patients with AIT can occur in 10–30% of cases [10]. A retrospective study on 28 patients with Hashimoto's thyroiditis and hematuria, proteinuria, or renal impairment

showed that the most common associated kidney diseases are membranous glomerulonephritis (20%), focal segmental glomerulosclerosis (20%), IgA nephropathy (15%), chronic glomerulonephritis (15%), minimal change disease (10%), and amyloidosis (5%). In 15% of the 28 patients, no specific diagnosis was made [11]. Other case reports revealed the less frequent connection between AIT and membranoproliferative glomerulonephritis and ANCA vasculitis [12 - 16]. Various hypotheses were considered to explain the underlying mechanism that links AIT to glomerular lesions and their variable presentation. The higher prevalence of membranous nephropathy (MN) suggests a plausible immunologic role of thyroid antigens, particularly thyroglobulin (TG) and thyroperoxidase (TPO). Both of them are released in the course of AIT and are found in subepithelial immune deposits, as part of the characteristic spikes of MN [16, 17]. At present, there are two possible mechanisms that can explain the immunologic role of thyroid antigens in the pathogenesis of MN: (1) in situ immune response against TG deposition at subepithelial level and (2) circulating immune complexes (TG-anti-TG) that can be trapped at subendothelial level due to increased glomerular permeability. As stated before, the pathogenicity of immune complexes in MN is related to their subepithelial localization, but how they could cross GBM remains unexplained. Most likely, immune complexes could dissociate in the subendothelial space and then they would reassemble on the subepithelial side. IgG4 is considered the main antibody subclass deposited in the course of idiopathic MN. Specific subclass of anti-TG and anti-TPO antibodies should be determined in patients with suspicious AIT-related glomerulopathy to distinguish between a clear diagnosis of idiopathic MN or a possible IgG4-mediated secondary form of MN. Moreover, IgG4 antibodies have low affinity for the antigen, which could explain the possible dissociation and reassociation of the IgG4 complexes through the GBM [18]. Other theories involve the mechanism of epitope spreading, a phenomenon that follows the primary immune

response against specific epitopes. When the immunodominant response fails to clear the target, the immune system mounts a broader inflammatory response against different epitopes either on the same or on different molecules. Therefore, immune-mediated glomerular disease would be caused by a subset of autoantibodies directed toward epitopes of TG or TPO as well as epitopes of glomerular antigens. This phenomenon may be relevant to the pathogenesis of kidney disease, since in Heymann nephritis (a murine experimental model of membranous glomerulonephritis) the onset of proteinuria correlates with intramolecular epitope spreading [19]. In addition, epitope spreading has already been demonstrated in experimental immunization with an immunogenic TG peptide, but has not been investigated in patients so far. [20]. The experimental Heymann model also suggests megalin (gp330) as a possible immunologic target involved in the immunopathogenesis of glomerular injury during AIT. Megalin is a large glycoprotein receptor expressed on thyrocytes in a TSH-dependent manner, but it is also expressed on the renal proximal tubular cells [21]. Megalin is a receptor that interacts with various intracellular adaptor proteins for intracellular trafficking and that functions cooperatively with other membrane molecules [21]. Megalin is involved in the uptake of glomerular filtered albumin and other molecules such as insulin, hemoglobin, vitamin D-binding protein, retinol-binding protein, and  $\beta$ 2-microglobulin. In addition, a number of toxic substances, such as glycated proteins (AGEs), myeloma light chain, and aminoglycosides, undergo megalin-mediated endocytosis, leading to cell damage [21]. AIT could determine a rupture of immune tolerance toward this self-antigen, thus causing an immune response on podocytes.

The relationship between AIT and ANCA vasculitis was shown by Lionaki and colleagues [22]. In their case-control study, they demonstrated that when ANCA vasculitis was diagnosed, as many as 40% of women had thyroid disease. Among men, the prevalence of thyroid disease was lower. Patients with positive

anamnesis for thyroid disease were more likely to have myeloperoxidase (MPO)-ANCA (86%) than proteinase 3-ANCA (14%) [22]. Both genetic predisposition and cross-reactivity between antigens have been hypothesized as potential mechanisms for this association. A functional polymorphism in the protein tyrosine phosphatase gene, the PTPN22 620W allele has been recognized as a predisposing factor for several autoimmune disorders, including AITD, Wegener's granulomatosis, and ANCA positivity [23 - 25]. PTPN22 is located on chromosome 1p13.3-13.1.10 and encodes an 807-amino acid protein that interacts with Csk, a tyrosine kinase that is involved in the intracellular signaling cascade following T-cell activation. A missense variation in the autoimmunity-predisposing allele results in gain of function that increases the threshold for T-cell receptor signaling [26]. As in other multifactorial processes, one or more environmental triggers are necessary for the full development of the disease. Occupational exposures to factors such as silica [27] showed an association with ANCA vasculitis, while infections such as *Yersinia enterocolitica* or retroviruses have been postulated to participate in the pathogenesis of AITD [25]. Eventually, cross reactivity between TPO and MPO may be another mechanism involved in the development of autoimmunity, due to the strong homology between amino acids 586-601 of TPO and amino acids 594-609 of MPO [28, 29].

Finally, renal diseases presenting as nephrotic syndrome can lead to the onset or the aggravation of preexisting hypothyroidism. The urinary loss of both protein-unbound (free) and protein-bound thyroid hormones, with consequent decreased serum levels of T4, T3, FT4, FT3, and major carrier proteins (thyroxine-binding protein, transthyretin, and albumin), is directly proportional to proteinuria. The practical consequence of this urinary loss is the increased requirements of the daily L-T4 replacement [30].

## **Case report**

---

A 24 year old female patient came with chief complaints of swelling of whole body since 20 days. Patient was apparently asymptomatic 20 days back, then she developed swelling of lower limbs and gradually progressed to generalized anasarca, including facial puffiness and peri-orbital edema. She complained of loose stools and vomiting, for past 5 days and also she had fever with chills for 2 days. Patient had history of Hair loss, Weight gain, dry skin, cold-intolerance since 1 year. There was no history of burning micturition or hematuria, She had regular menstrual cycles, but complained of heavy bleeding for which she used medication. There is no history of abortions. She developed hypothyroidism, during her pregnancy, 18 months ago. And she is on eltroxin since then. She underwent C-section 18 months ago. She was not a known case of hypertension, diabetes mellitus, epilepsy, CVA, CAD.

**On examination** - The patient was of heavy-built short stature, with dry skin, with macro glossia, with generalized anasarca, with pitting type of edema. Patient had no pallor, no icterus, no cyanosis, no clubbing, no koilonychia, no lymphadenopathy. Her temperature was 98.4<sup>0</sup> F, pulse rate 100/mt, BP 130/80 mm Hg CVS, CNS and Respiratory system examination was normal, abdomen was soft with no organomegaly.

**On Investigation** - Hb-14.10 gm/dl, RBC count 7.2 mill/cumm, WBC count 8400 cells/cumm with Neutrophils - 72%, Lymphocytes - 24%, Eosinophils - 2%, Basophils - 0%, Monocytes - 2%, Platelet count - 1.8 lakhs/cu mm. ESR 1<sup>st</sup> hr - 20 mm, Hepatitis B and C and HIV was negative, Random Blood Sugar - 109 mg/dl, Blood - Urea 37 mg/dl, S.Creatinine - 0.7 mg/dl, S. Sodium 141 mmol/l, S. Potassium 4 mmol/l, S. Chloride 106 mmol/l, total protein 4.4 gm/dl, Serum albumin - 1.8 gm/dl, Complete Urine Examination (CUE) - proteinuria (2+), with 5-6 RBC casts, Calcium Oxalate crystals, UPCR 15.47, Spot Urine Protein - 2748 mg/dl, Spot Urine creatinine - 177 mg/dl, 24hrs Urinary protein - 17327 mg/dl, Urine for C/S - Sterile, Stool for Ova cyst -Negative, LFT - Normal,

**FASTING LIPID PROFILE** - Serum triglycerides – 231 mg/dl, LDL – 183 mg/dl, Total Cholesterol – 278 mg/dl, HDL - 58 mg/dl, ESR-10 mm/hr, ECG-Sinus Tachycardia, **THYROID PROFILE** - T3- 0.53 ng/dl (0.40-1.81), T4-7.13 microgm/dl, TSH-15.06 micro IU/ML, Anti TG antibodies - 9.60 (normal <4.11 IU per ml), Anti TPO antibodies - 64.04 (<5.6 IU per ml) and Anti DS-DNA-Negative (12.44), USG NECK-Mild thyromegaly with mild heterogenous echotexture and increased vascularity-thyroiditis, FNAC of thyroid gland - auto immune thyroiditis – showed clusters of Follicular epitheliul cells with plenty of lymphocytes against blood-mixed scanty colloid back ground, USG Abdomen showed kidney size Rt-10.0 X 3.8cm, Lt-11.0 X 5.2cm), Renal biopsy was not done as patient did not give consent, Chest X-ray – PA view – Normal, ECG – revealed low voltage complexes.

A diagnosis of Hashimoto's Thyroiditis with Nephrotic Syndrome was made.

### **Treatment given**

- 1) Tablet – Cifran-CT 1 BD
- 2) T. Eltroxin – 100 mcg OD
- 3) T. Sporlac DS TID
- 4) Tablet – Wysolone 100 mg (2 mg/kg body weight), in divided doses
- 5) Tablet – Shellcal 500 mg OD
- 6) Tablet – Buscogast 1 TID
- 7) Tablet – Metrogyl 400mg 1 TID
- 8) Fluid Restriction to less than 2Ltrs per day
- 9) Strict Intake and Output charting and weight monitoring is done.

The patient was kept on thyroxine – 100 mcg/day, along with steroids 2 mg/kg body weight. After 15 days the 24 hrs urinary proteins decreased to – 5.0 Gm/day, which was 17.327 Gm/day. After a month, it is further decreased to 1.0 Gm/day.

### **Discussion**

In a recent meta-analysis by Liu, et al. [31] assessed the efficacy of thyroid hormone replacement therapy for nephrotic syndrome

patients associated with non-thyroidal illness syndrome. They found that thyroid hormone replacement increased the remission rate of the nephrotic syndrome and was not associated with any side effect.

Clinical hypothyroidism was defined as elevated TSH levels (>10 mIU/L) along with low or normal levels of serum T4. Subclinical hypothyroidism was defined as mildly elevated TSH levels (5–10 mIU/L) along with normal levels of serum T4 [32]. In their study, levels of TSH were higher in patients with low serum albumin and higher proteinuria. This finding can be explained by the fact that low serum albumin levels directly indicate higher urinary loss of proteins, thus higher loss of thyroid binding hormones. TSH levels are in turn increased to compensate for the urinary loss [33]. However, overt hypothyroidism that is clinically relevant was not present. Similar observations were made by Gilles et al in their study of hypothyroidism in patients of proteinuria [34]. However, they had excluded anti-TPO antibody positive patients from their study.

On histopathological examination of renal biopsy, the most common finding among the hypothyroid patients with nephrotic syndrome was membranous glomerulopathy, found in 48% of their study subjects [35 - 38]. The deposition of circulating immune complexes has been implicated in pathogenesis [39]. However, in their study 72% of patients with membranous nephropathy were anti-TPO antibody negative. The mechanism of autoimmunity causing this type of nephropathy could probably be explained by other antibodies not tested in their study.

There have been few studies showing the association of autoimmune hypothyroidism with various types of nephrotic syndrome. A retrospective study on 28 patients with Hashimoto's thyroiditis revealed that the most common associated kidney disease was membranous glomerulonephritis. Hashimoto's thyroiditis has also been found in patients of lupus nephritis, minimal change disease, IgA

nephropathy, membranoproliferative glomerulonephritis and focal segmental glomerulosclerosis [40, 41]. In their study, thyroid autoantibodies were positive in 41.7% of study subjects. Although there was no documented evidence of an association of anti TPO antibodies with nephrotic syndrome or any other form of renal dysfunction, a few mechanisms have been postulated for the possible association. Autoimmunity serves as the strongest predictor. Immune complex deposits have been found in basement membrane of thyroid follicular epithelium and glomeruli in some reported patients of Hashimoto thyroiditis and membranous glomerulopathy [42].

Factors supporting the autoimmune pathogenesis of renal and thyroid dysfunction include their common association with other autoimmune diseases such as type I diabetes [43]. The presence of deposits of immunoglobulins and thyroglobulin in the glomeruli of some patients is also an indirect indicator of common pathogenesis of both renal and thyroid dysfunction.

Glomerular disease was found in many autoimmune conditions such as lupus nephritis, ANCA associated vasculitis that can also be associated with autoimmune thyroid disease. In a study conducted by Pyne, et al., the prevalence of hypothyroidism in SLE patients was greater than that of normal population [44]. This is supported by higher prevalence of Anti-TPO and anti-thyroglobulin antibodies in their study. In their study, 16% patients with positive anti-TPO antibodies had lupus nephritis [45].

The occurrence of Graves' disease and Hashimoto's thyroiditis in the same family and the increased prevalence of autoantibodies in relatives of patients with Hashimoto's thyroiditis are well documented, [46, 47]. The association of immune complex nephritis with Hashimoto's thyroiditis as in the propositus is rare. [48], Membranoproliferative glomerulonephritis with the deposition of immune complexes with thyroglobulin as the antigen was reported in

these patients. In one case, thyroglobulin was also shown in the circulating immune complexes, with a positive correlation between the serum concentrations of these complexes and the severity of the disease [48]. It was suggested that the glomerular disease was caused by trapping of nephritogenic immune complexes from the blood stream. In their propositus thyroglobulin was found in the glomerular capillary clumps but not in the circulating immune complexes. Glomerular deposits are formed in situ by the reaction of free antibody with a fixed antigenic constituent of the glomerular capillary wall [49]. Proteinuria alone, without the nephrotic syndrome, has been reported in two of 27 patients with Hashimoto's thyroiditis [50], but the natural course of this type of kidney disease is unknown. Some patients with kidney disease underwent total thyroidectomy with the aim of eliminating the antigen. In these cases the proteinuria was not eliminated during a follow up course of several months [51, 52], but the circulating antimicrosomal and antithyroglobulin antibodies disappeared. [52, 53].

A diagnosis of Hashimoto's Thyroiditis with Nephrotic Syndrome was made. Renal biopsy was not done.

## **Conclusion**

In this case report we find correlation between nephrotic syndrome and thyroid function abnormalities. Due to major renal handling of thyroid hormones, all patients with nephrotic range proteinuria are at risk of developing clinical and subclinical hypothyroidism. Due to some overlapping features of both the diseases such as facial puffiness, weight gain and fatigue, hypothyroidism can easily be missed unless it becomes severe enough to cause gross changes in the patient's appearance and starts to impair the cardiovascular and other major organ systems of the body. If left untreated, hypothyroidism can further impair renal functioning. Our case report tries to establish a correlation between thyroid autoimmunity and nephrotic syndrome. Thus, a high index of suspicion should be kept in all

patients with nephrotic syndrome and thyroid function tests, while tests for antibodies against thyroid antigen should be a part of routine screening in these patients. These patients may require increased dose of thyroxine for hypothyroidism, because of urinary protein loss [54].

In our case hypothyroidism is detected first, then after we investigated the case thoroughly, as we saw the association of hypothyroidism causing nephrotic syndrome. A diagnosis of Hashimoto's Thyroiditis with Nephrotic Syndrome was made. Renal biopsy was not done. She responded to corticosteroids.

## References

1. Feinstein EI, Kaptein EM, Nicoloff JT, Massry SG. Thyroid function in patients with nephrotic syndrome and normal renal function. *Am J Nephrol.*, 1982; 2: 70–76.
2. Junglee NA, Scanlon MF, Rees DA. Increasing thyroxine requirements in primary hypothyroidism: don't forget the urinalysis. *J Postgrad Med.*, 2006; 52: 201–203.
3. Suher M, Koc E, Ata N, Ensari C. Relation of thyroid dysfunction, thyroid autoantibodies, and renal function. *Ren Fail.*, 2005; 27: 739–742.
4. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. *Eur J Endocrinol.*, 2009; 160: 503–515.
5. Hull RP, Goldsmith DJ. Nephrotic syndrome in adults. *BMJ*, 2008; 336: 1185–1189.
6. Deepak Jain, Hari Krishan Aggarwal, YM Pavan Kumar, and Promil Jain. Evaluation of thyroid dysfunction in patients with nephrotic syndrome; *Med Pharm Rep.*, 2019 Apr; 92(2): 139–144.
7. Benvenga S, Trimarchi F. Changed presentation of Hashimoto's thyroiditis in North-Eastern Sicily. *Thyroid*, 2008; 18(4): 429–41.
8. Fallahi P, Ferrari SM, Ruffilli I, Elia G, Biricotti M, Vita R, et al. The association of other autoimmune diseases in patients with autoimmune thyroiditis: review of the literature and report of a large series of patients. *Autoimmun Rev.*, 2016; 15(12): 1125–8.
9. Santoro D, Vadalà C, Siligato R, Buemi M and Benvenga S; Autoimmune Thyroiditis and Glomerulopathies. *Front. Endocrinol.*, 2017; 8: 119. doi: 10.3389/fendo.2017.00119
10. Ronco P, Debiec H. Pathophysiological lessons from rare associations of immunological disorders. *Pediatr Nephrol.*, 2009; 24(1): 3–8.
11. Koçak G, Huddam B, Azak A, Ortabozkoyun L, Duranay M. Coexistent findings of renal glomerular disease with Hashimoto's thyroiditis. *Clin Endocrinol.*, 2012; 76: 759–62.
12. Valentin M, Bueno B, Gutierrez E, Martinez A, Gonzalez E, Espejo B, et al. Membranoproliferative glomerulonephritis associated with autoimmune thyroiditis. *Nefrologia.*, 2004; 3: 43–8.
13. Gurkan S, Dikman S, Saland MJ. A case of autoimmune thyroiditis and membranoproliferative glomerulonephritis. *Pediatr Nephrol.*, 2009; 24(1): 193–7.
14. Kageyama Y, Hamaguchi K. Myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)-positive microscopic polyarteritis (MPA) associated with Hashimoto's thyroiditis and increased serum rheumatoid factor. *Clin Exp Nephrol.*, 2000; 4: 335–40.
15. Thajudeen B, John SG, Ossai NO, Riaz IB, Bracamonte E, Sussman AN. Membranous nephropathy with crescents in a patient with Hashimoto's thyroiditis: a case report. *Medicine*, 2014; 93(8): e63.
16. Shima Y, Nakanishi K, Togawa H, Obana M, Sako M, Miyawaki M, et al.

- Membranous nephropathy associated with thyroid-peroxidase antigen. *Pediatr Nephrol.*, 2009; 24(3): 605–8.
17. Jordan SC, Buckingham B, Sakai R, Olson D. Studies of immune-complex glomerulonephritis mediated by human thyroglobulin. *N Engl J Med.*, 1981; 304: 1212–5.
  18. Oliveira DB. Membranous nephropathy: an IgG4-mediated disease. *Lancet*, 1998; 351: 670–1.
  19. Shah P, Tramontano A, Makker SP. Intramolecular spreading in Heymann nephritis. *J Am Soc Nephrol.*, 2007; 18: 3060–6.
  20. Thrasyvoulides A, Lymberi P. Evidence for intramolecular B-cell epitope spreading during experimental immunization with an immunogenic thyroglobulin peptide. *Clin Exp Immunol.*, 2003; 132: 401–7.
  21. Christensen EI, Birn H, Storm T, Weyer K, Nielsen R. Endocytic receptors in the renal proximal tubule. *Physiology (Bethesda)*, 2012; 27(4): 223–36.
  22. Lionaki S, Hogan SL, Falk RJ, Joy MS, Chin H, Jennette CE, et al. Association between thyroid disease and its treatment with ANCA small-vessel vasculitis: a case-control study. *Nephrol Dial Transplant.*, 2007; 22: 3508–15.
  23. Brand O, Gough S, Heward J. HLA, CTLA-4 and PTPN22: the shared genetic master-key to autoimmunity? *Expert Rev Mol Med.*, 2005; 7: 1–15.
  24. Mustelin T. Are other protein tyrosine phosphatases than PTPN22 associated with autoimmunity? *Semin Immunol.*, 2006; 18: 254–60.
  25. Corapçioğlu D, Tonyukuk V, Kiyani M, Yilmaz AE, Emral R, Kamel N, et al. Relationship between thyroid autoimmunity and *Yersinia enterocolitica* antibodies. *Thyroid*, 2002; 12: 613–7.
  26. Martorana D, Maritati F, Malerba G, Bonatti F, Alberici F, Oliva E, et al. PTPN22 R620W polymorphism in the ANCA-associated vasculitides. *Rheumatology (Oxford)*, 2012; 51: 805–12.
  27. Hogan SL, Cooper GC, Savitz DA, Nylander-French LA, Parks CG, Chin H, et al. Association of silica exposure with ANCA-associated glomerulonephritis: a population-based case-control study in the southeastern United States. *Clin J Am Soc Nephrol.*, 2007; 2: 290–9.
  28. Hobby P, Gardas A, Radomski R, McGregor AM, Banga JP, Sutton BJ. Identification of an immunodominant region recognized by human autoantibodies in a three-dimensional model of thyroid peroxidase. *Endocrinology*, 2000; 141: 2018–26.
  29. Haapala AM, Hyöty H, Parkkonen P, Mustonen J, Soppi E. Antibody reactivity against thyroid peroxidase and myeloperoxidase in autoimmune thyroiditis and systemic vasculitis. *Scand J Immunol.*, 1997; 46: 78–85.
  30. Benvenga S, Vita R, Di Bari F, Fallahi P, Antonelli A. Do not forget nephrotic syndrome as a cause of increased requirement of levothyroxine replacement therapy. *Eur Thyroid J*, 2015; 4(2): 138–42.
  31. Liu H, Yan W, Xu G. Thyroid hormone replacement for nephrotic syndrome patients with euthyroid sick syndrome: a meta-analysis. *Ren Fail.*, 2014; 36: 1360–1365.
  32. Cooper DS. Clinical practice. Subclinical hypothyroidism. *N Engl J Med.*, 2001; 345: 260–265.
  33. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. *Indian J Endocrinol Metab.*, 2012; 16: 204–213.
  34. Gilles R, den Heijer M, Ross AH, Sweep FC, Hermus AR, Wetzels JF. Thyroid function in patients with proteinuria. *Neth J Med.*, 2008; 66: 483–485.



35. Mariani LH, Berns JS. The renal manifestations of thyroid disease. *J Am Soc Nephrol.*, 2012; 23: 22–26.
36. Salomon MI, Di Scala V, Grishman E, Brenner J, Churg J. Renal lesions in hypothyroidism: a study based on kidney biopsies. *Metabolism*, 1967; 16: 846–852.
37. Valentin M, Bueno B, Gutiérrez E, Martínez A, González E, Espejo B, et al. Membranoproliferative glomerulonephritis associated with autoimmune thyroiditis. *Nefrologia.*, 2004; 24 (Suppl 3): 43–48.
38. Grcevska L, Polenakovic M, Petrussevska G. Membranous nephropathy associated with thyroid disorders. *Nephron*, 2000; 86: 534–535.
39. Shima Y, Nakanishi K, Togawa H, Obana M, Sako M, Miyawaki M, et al. Membranous nephropathy associated with thyroid-peroxidase antigen. *Pediatr Nephrol.*, 2009; 24: 605–608.
40. Santoro D, Vadalà C, Siligato R, Buemi M, Benvenega S. Autoimmune Thyroiditis and Glomerulopathies. *Front Endocrinol (Lausanne)*, 2017; 8: 119.
41. Enriquez R, Sirvent AE, Amorós F, Andrada E, Cabezuelo JB, Reyes A. IgA nephropathy and autoimmune thyroiditis. *Clin Nephrol.*, 2002; 57: 406–407.
42. Jordan SC, Johnston WH, Bergstein JM. Immune complex glomerulonephritis mediated by thyroid antigens. *Arch Pathol Lab Med.*, 1978; 102: 530–533.
43. Dizdar O, Kahraman S, Gençtoý G, Ertoý D, Arici M, Altun B, et al. Membranoproliferative glomerulonephritis associated with type 1 diabetes mellitus and Hashimoto's thyroiditis. *Nephrol Dial Transplant.*, 2004; 19: 988–989.
44. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. *Ann Rheum Dis.*, 2002; 61: 70–72.
45. Deepak Jain, Hari Krishan Aggarwal, YM Pavan Kumar, and Promil Jain. Evaluation of thyroid dysfunction in patients with nephrotic syndrome. *Med Pharm Rep.*, 2019 Apr; 92(2): 139–144.
46. Roitt IM, Doniach D. Reassessment of studies on the aggregation of thyroid autoimmunity in families of thyroiditis patients. *Clin Exp Immunol.*, 1967; 2(suppl): 727-36.
47. Burek LC, Hoffman WH, Rose NE. The presence of thyroid autoantibodies in children and adolescents with autoimmune thyroid disease and their siblings and parents;. *Clin Immunol Immunopathol.* 1982; 25: 395-404.
48. Jordan SC, Buckingham B, Saka R, Olson D. Studies of immune complex glomerulonephritis mediated by human thyroglobulin. *N Engl J Med.*, 1981; 304: 1212-5.
49. Couser WC. What are circulating immune complexes doing in glomerulonephritis? *N Engl J Med.*, 1981; 306: 1230-1.
50. Churchill DN, David N. Proteinuria in Hashimoto's thyroiditis. *N Engl J Med.*, 1981; 305: 1286.
51. O'Regan S, Fong JSC, Kaplan BS, deChardarevian JP, Lapointe N, Drummond KN. Thyroid antigen-antibody nephritis. *Clin Immunol Immunopathol.*, 1976; 6: 341-6.
52. Horvath F, Teague P, Gaffney EF, Mars DR, Fuller TJ. Thyroid antigen associated immune complex glomerulonephritis in Graves' disease. *Am J Med.*, 1979; 67: 901-4.
53. Shuper, Leathem, Pertzalan, Eisenstein, Mimouni. Familial Hashimoto's thyroiditis with kidney impairment. *Archives of Disease in Childhood*, 1987; 62: 811-814.
54. Iglesias P, Díez JJ. Thyroid dysfunction and kidney disease. *Eur J Endocrinol.*, 2009; 160: 503– 515.