Chapter

Recent Advances in Clinical Diagnosis and Pharmacotherapy Options of Membranous Nephropathy in Iraqi Patients

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Abstract

Membranous nephropathy (MN) is one of the various glomerular diseases causing nephrotic syndrome, also referred to as membranous glomerulopathy. It can be diagnosed at any age in general, and males are more often affected than females (with the sex ratio being 2–3:1). Membranous nephropathy is a relatively rare disease in adults (approximately half of all cases are common in older White adults). Statistical analysis shows that 80% of patients with MN have high creatinine level, dyslipidemia, hypoalbuminemia, proteinuria more than (3.5 g/day), and fluid retention (edema), while 20% with asymptomatic with non-nephrotic levels of proteinuria (< 3.5 gram/day) involves the reaction of an inflammatory process in the basement membrane. It can be distinguished from nephritic syndromes by the absence of active sediments, hematuria, and red cell casts in urine microscopy. The two main causes of nephrotic range proteinuria are the loss of the anionic charge barrier in the membrane and podocyte destruction, which results in albuminuria. The field has advanced greatly and quickly over the past 10 years thanks to the development of cutting-edge instruments for disease diagnosis, classification, monitoring, and treatment. This core curriculum aims to serve as both a broad guide for the clinical management of disease and an overview of recent developments in the field. In the review, we critically summarized different diagnosis biomarker therapies used for the treatment of MN patients in Iraq. These groundbreaking discoveries were swiftly applied to clinical diagnosis and management. The diagnosis and treatment monitoring processes benefited significantly from significant advancements in detection techniques.

Keywords: idiopathic membranous nephropathy, membranous nephropathy

1. Introduction

Membranous nephropathy (MN), a glomerular disorder, is the most common cause of nephrotic syndrome in Caucasian individuals who do not have diabetes. The

majority of MN cases are primary (idiopathic), while the remainder are related to systemic illness, pathogen exposure, or medications use [1]. Membranous nephropathy develops when the glomeruli, which are small blood capillaries in the kidney that are responsible for ultrafiltration of waste products and other polymers from the blood, suffer injury and thicken. As a result, a large amount of protein infiltration into the urine (proteinuria) with an increase in single nephron glomerular filtration rate (SNGFR) and increase in glomerular capillary hydraulic pressure (GCHP) [2]. The loss of these proteins eventually results in the nephrotic syndrome's signs and symptoms. However, the kidney has a huge number of filtering cells or units known as glomeruli. There were only three layers of capillary walls in these glomeruli:

- Endothelial cells are a single layer of cells that lines an inner blood artery. The pores of this layer of about 70 nm in diameter are used to prevent the filtration of blood cells such as RBCs.

- Podocytes of Bowman's capsule are specialized epithelial cells that compose the visceral layer of the Bowman's capsule.

- Glomerular basement membrane (GBM) is a thin membrane that separates two cell layers, endothelial and epithelial. GBM is a thin layer that is made up of collagen, proteoglycans, heparan sulfate, and laminin. This layer assists negatively charged molecules in moving across the membrane. These three layers are necessary for the kidneys to function properly, and they can be damaged by inflammation or other factors [3, 4]. Damage to the podocyte layer can lead to high levels of protein infiltering into the urine from the kidneys. The majority of MN patients show circulating IgG4 antibodies to the podocyte antigens thrombospondin type 1-domain-containing 7A (THSD7A) (3–5%), phospholipase A2 receptor (PLA2R) (70–85%), and about 10% of another podocyte antigen that resembles PLA2R. To reduce the excessive levels of protein excretion in urine, all individuals with idiopathic MN should be given a classic treatment as soon as they are diagnosed. Immunosuppressive medication is often only used for patients who continue to experience nephrotic range proteinuria in spite of receiving conservative management or not. Combinations of alkylating drugs or inhibitors of calcineurin with RITUXAN® are considered as examples of immunosuppressive medications for the treatment of primary MN [5, 6].

2. Signs and symptoms of MN

Membrane nephropathy occurs gradually, so you may not notice any abnormal signs. Some patients may not exhibit any symptoms until they develop renal disease, despite the fact that many patients experience mild symptoms at the outset of the disease [7]. MN symptoms and signs include:

- lack of appetite;

- swelling in the legs and ankles or edema;

- proteinuria;

- tiredness;
- high fat in the blood;
- weight gaining;
- problems in the blood pressure;
- decreased level of albumin in the blood.

Or symptoms and signs due to complications include:

- blood in the urine
- abrupt shortness of breath, which could be caused by a blood clot issue, and a sudden pain between the upper belly and the middle back.

A small percentage of MN patients report no symptoms; in these cases, clinicians may discover symptoms either during routine office visits or after evaluating certain biochemical indicators. Most individuals (60–70%) will have symptoms of MN, and 1–3% having proteinuria in the subnephrotic range less than 3.5 g/day. One to three percent of MN patients also experience microscopic hematuria. Only a small percentage of patients experience hypertension or renal failure, and older people are more likely to experience these conditions. About 7% prevalence of venous thrombophlebitis and dyslipidemia has been found in MN. The rate of MN is high, and it is challenging to predict how the condition will develop naturally. Up to 30% of cases are known to have spontaneous remission. The percentage of patients who enter spontaneous remission is significantly lower. 2 to 3% of patients either have ongoing proteinuria with stable kidney functions or will eventually experience renal failure. The risk of fatal thromboembolic and cardiovascular events rises even in patients who do not develop nephrotic disease. If kidney function rapidly decreases, a secondary disorder such as interstitial nephritis or renal vein disease may be present [8].

3. Causes of MN

Frequently, some types of autoimmune activity cause membranous nephropathy (primary membranous nephropathy). Immune complexes accumulate on the glomerular basement membrane (GBM) and cause GBM thickening, which is known as membranous nephropathy. Primary MN is typically unknown, although secondary MN causes the following:

- Autoimmune diseases, such as lupus erythematosus;
- Infection by some viruses such as (hepatitis B and C, HIV, and syphilis) or infection with parasites such as plasmodium falciparum and leishmania;
- Drugs include thiol drugs such as D-penicillamine, ionic chemical drugs (salt of gold,), and nonsteroidal medications (anti-inflammatory) such as ibuprofen and piroxicam [9];

- Solid cancers such as hematological and lung cancers;

- Recently, COVID-19 infection with corona viruses can cause a broadspectrum of glomerular diseases (membranous nephropathy) and acute tubular disease. This can even be linked with anti-PLA2R positive. Membranous nephropathy has been reported following anti-COVID-19 mRNA vaccination. In the primary membranous nephropathy, flares after Covid-l9 vaccination have been reported in the literature [10].

4. The possibility of developing MN

1. Having health issues could harm the kidneys. Membranous nephropathy is more likely to occur in people with specific illnesses and conditions such as lupus and other autoimmune disorders [11].

2. Use of certain medications as mentioned under subtitle causes.

3. Being exposed to specific viral diseases as mentioned in the paragraph above [2]. Recently, it is likely that acute tubular injury and collapsing glomerulopathy are frequency caused by specific viral COVID-19.

4. Genetic history. The likelihood of developing membranous nephropathy is increased by specific hereditary variables. MN is not a typical hereditary disease in Mendelian terms. However, primary membranous nephropathy is associated with certain HLA class II immune response genes [12].

5. Complications

Membranous nephropathy has a number of complications that include the following:

- High-fat levels: people with membrane nephropathy frequently have high levels of both cholesterol (Cho) and triglycerides (TGs), which dramatically increase the risk of heart disease, owing mainly to impaired clearance and, to a lesser extent increased biosynthesis [13].

- Blood clot: Patients who suffer from proteinuria lose proteins in their urine, which aids in preventing blood clotting. Blood clots that form in deep veins or that go to the lungs are more likely to form in patients, and this leads to deep vein thrombosis, renal vein thrombosis, and pulmonary embolism.

- High blood pressure: Both soft retention and accumulation of waste in the blood (uremia) can increase blood pressure.

- Microbial infections: When proteinuria causes a reduction in immune system proteins (antibodies) that guard against infection, patients are more vulnerable to infections.

- Nephrotic syndrome: This condition is characterized by high levels of protein excreted in the urine, decreased levels of protein in the blood, high serum cholesterol, and swelling around the eyes known as edema, or in the feet, or abdomen.

- Acute kidney injury: Waste product may build up quickly in the blood in cases of severe kidney filtering units (glomeruli) damage, and the patient may need an urgent diagnosis to bring out any waste from the blood.

- Chronic kidney disorders: Due to the patient's kidneys gradually losing function over time, they may eventually need dialysis or a kidney transplant [13, 14].

6. Epidemiology

Adults with MN have a higher frequency of nephropathy than those with focal segmental glomerulosclerosis (FSGS) [15]. In White people over 40 years, it is the most frequent cause of primary nephrotic syndrome. In 2002, a report showed patterns of glomerular diseases in Iraq and other Arabic countries as shown in **Table 1**. The most frequently diagnosed lesion in our patients with primary glomerular disease is FSGS [16]. This Iraqi study indicates that the histology of the patients' biopsies with proteinuria exhibits certain patterns that might reflect glomerular pattern illnesses in Iraq and might not be distinct compared to those in the other Arab nations and Middle Eastern nations in particular. In the USA, the peak incidence occurs between 50 and 60 years [13, 17]. MN is more prevalent in men than in women, and the latter often has a favorable outcome in women. When MN is diagnosed in young women, lupus nephritis should be suspected. Approximately 75% of the MN cases occur as a primary disease and about 25% as secondary MN that is associated with autoimmune diseases (e.g., systemic lupus erythematosus (SLE)), infection with hepatitis B or hepatitis C, HIV, and less commonly Epstein–Barr virus (EBV) that can also cause acute or chronic kidney disease. Parasitic agents which cause malaria or schistosomiasis are potential causes of secondary MN, cancer (breast cancer), drugs, and toxin as aforementioned in paragraph [18].

In children, MN is less common due to secondary causes, accounting less than 7% of biopsies and is associated with other diseases such as hepatitis B, autoimmune, or thyroid diseases. It may also develop in conjunction with other types of glomerulonephritis (focal segmental glomerulosclerosis (FSGS), IgA nephropathy (Berger's

Country	No. of patients	MCD	FSGS	MPGN	MGN	PGN*
Iraq	500	76(17.07%)	117(26.25%)	72(16.17%)	65(14.60%)	100(22.47%)
Sudan	40	7(17%)	5(12%)	—	13(33%)	15(38%)
Saudi Arabia	148	2(1.3%)	45(30.4%)	22(14.8%)	16(10.8%)	63(42.5%)
Tunisia	304	49(16%)	49(16%)	51(16,9%)	64(21%)	91(30%)

**PGN: primary glomerulonephritis, FSGS: focal segmental glomerulosclerosis, MCD: minimal change disease, MPGN: membranoproliferative glomerulonephritis, MGN: membranous glomerulonephritis.*

Table 1.
Relative frequency of various types of glomerular lesions among adults in different countries.

disease), and lupus nephritis) [12, 19]. According to an Iraqi study, Denovo Iraqi patients with MN are at the last stage of renal disorders as a result of a distinct main renal ailment. Children having transplanted kidneys are more likely to experience it [20]. It was discovered in 48 of 530 pediatric allograft biopsies in one study. It typically happens many years after a kidney transplant, as in this instance. The interim period for de novo MN ranged from 63 to 102 months, in two significant retrospective studies. Despite this infestation, other reports described the de novo MN at an early onset [13]. Recently, it was discovered that children with early-onset MN had circulating antibodies reactive with bovine serum albumin (BSA) in their blood and also had immunological deposits in the kidneys. It is suggested that ingestion of modified albumin (BSA) will lead to the development of anti-BSA AB and will attach to anionic residues in the BM, where it will act as a planted antigen for the development of immunological accumulations in situ [21, 22].

7. Pathogenesis

Membranous nephropathy, also known as membranous glomerulonephritis (MGN) (**Figure 1**) [22], was first described as a type of glomerular disease by Bell in 1946. In adults, it is accounts 20–30% of idiopathic nephrotic syndrome and about 1–9% in children. In large majority of cases, this condition occurs in a primary ("idiopathic") form, but the disease has been related to a wide variety of conditions (secondary) in approximately 20–25% of adults and 80% of children with MGN. Circulating autoantibodies bind to an autoantigen on the surface of the podocytes, resulting in in situ immune complex formation that activates the lectin complement pathway and causes podocyte injury and proteinuria. Two mechanisms presumed responsible for the development and localization of the deposits along the GBM are those of in situ immune complex formation in the subepithelial capillary wall or that of circulating immune complexes being deposited in that location [6].

According to experimental findings, most immune complexes are formed in situ by circulating antibodies binding to antigens normally found in the glomerulus or to extrinsic antigens previously planted as free antigens in the subepithelial area. Primary human MGN appears to be mostly an autoimmune disease characterized by the

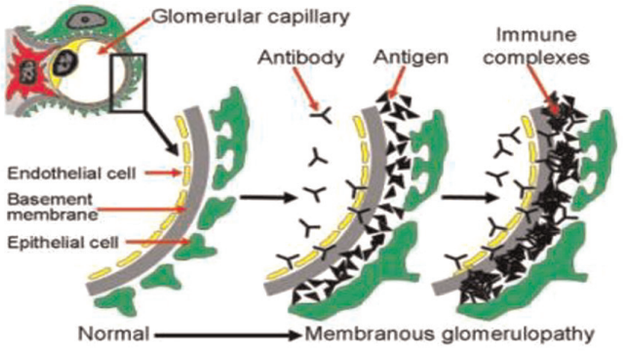

Figure 1.
shows a glomerulus, compared to normal on the left and one affected by MN on the right. On the right, the dark spots are collections of Ag-Ab complexes that accumulate between layers of filters and then lead to thick. The green color is podocytes caused by damaged part of the filter by the immune system and stopped working properly.

formation of glomerular immune complexes in situ. Over 70–80% of primary MGN patients have autoantibodies directed against PLA2R expressed in podocytes and proximal tubules. These circulating PLA2R autoantibodies are of the IgG4 subtype [14].

- plasma levels correlate with:

*Disease activity.
*Therapeutic response.
*The prediction of the risk of posttransplantation recurrence.
**2018 7A (THSD7A), further expanding the role of autoimmunity in these patients.

***In a subset of patients with MGN, all-immune response appears to play a role in developing MGN. Neutral endopeptidase (NEP), expressed in podocytes and proximal tubular brush border, has been set as the target antigen (Ag) of antibodies accumulated in the epithelial space in patients with antenatal MN. In these cases, it is likely that the anti-NEP antibodies produced by the mother are transplacentally transferred to her child with genetic deficiency of NEP [13, 21].

*Some patients with Pompe disease and mucopolysaccharidosis IV receiving recombinant α glucosidase and aryl sulfatase B, respectively, also develop alloimmune responses resulting in MGN. De novo MGN in allograft also appears to be an alloimmune response. Conditions associated with secondary MGN include as those in **Table 2** [23].

Secondary forms of MGN typically lack circulating PLA2R, but a small subset of patients with hepatitis B, hepatitis C, malignant neoplasm, and sarcoidosis have circulating serum PLA2R. While this may be coincidental, it also raises the possibility that "primary" MGN is triggered by an underlying disease. The underlying disease and how it is treated can have a significant impact on the natural history and overall prognosis of MGN. When secondary MN is caused by drugs, toxic substances, or infections, removing the etiologic agent often results in the clinical symptoms disappearing and the renal lesion healing. The nephrotic syndrome may abate and the glomerular changes regress after resection and treatment of a malignant tumor. In patients with membranous lupus nephritis, the course is indolent, whereas those who develop a superimposed anti-GBM antibody disease undergo a rapid progression to renal failure.

group	common	uncommon
Parasitic diseases	Hepatitis	Hepatitis C, malaria, filariasis
Immune disease	Systematic lupus Erythermatosus, Diabetes mellitus	Hashimoto's disease, Graves' disease, small bowel enteropathy syndrome, anti-GBM and ANCA positive crescentic GN.
Drug/toxin or vaccine	Gold, penicillamine and covid vaccine	Mercury, hydrocarbons, formaldehyde
Other	renal transplantation or Tumor	Sickle cell disease, angiofollicular lymph node hyperplasia

Table 2.
Condition associated with membrane nephropathy.

8. Diagnosis of MN

Membranous nephropathy may not manifest any clinical symptoms. A routine urine test for another health issue may reveal that the patient has high levels of protein in the urine in this case. If the patient has no signs or symptoms of protein in the urine, a medical physical exam should be done, and blood pressure should be measured. The following tests may be performed:

8.1 A urine test (urinalysis)

- Microscopic examination of the urine sample: In moderate cases, urinalysis may show proteinuria without any formed elements in the sediment. Urine microscopy is often nephrotic, with fat drops and fatty casts. But it is important to keep in mind that urine sediment analysis functions extremely well as a urinary "biomarker" for a number of acute renal disorders (AKD) [24, 25].

- Urine protein test: This test is done by collecting urine sample for 24 hours and measuring the concentration of protein in the urine. This test is used for screening purposes, and urine protein to creatinine ratio and results can be adequate [26].

- Clearance of creatinine (CCr) test: This test is more reliable for patients with renal diseases and can be done by collecting urine sample for 24 hours then analysis. CCr is influenced by race and gender. The concentration of creatinine in vegetarian patients or those suffering from muscle wasting (in starvation case) can differ from general individuals

- Complement levels Urinary C5b-9 [27, 28].

8.2 Blood tests

Blood test measures either plasma or serum in order to give a numeric value that directly indicates renal function. These tests include

- Routine tests creatinine, blood urea nitrogen, lipid profile, and Cystatin C.

- Immunoassay: anti-double-strand DNA (dsDNA) can be done if the reaction of antinuclear antibody testing gives a positive result.

- Serological tests include hepatitis B and C, syphilis, and HIV [15, 29].

8.3 Imaging test

- The noninvasive diagnostic imaging process is known as computed tomography (CT). This test may be done with or without contrast. This test can offer a lot of detail about the kidneys compared with normal kidneys, such as injuries, various kidney diseases, and an accumulation of fluid and stones in the kidney [29, 30].

8.4 Renal biopsy

- A small fragment of the kidney is removed by the histopathologist. This test is required to confirm the details of the information for diagnosis. It can reveal the kind of kidney illness, the degree of renal damage, and the potential effectiveness of various treatments.

8.4.1 Microscopic (histological) description

- Stage 1: Glomeruli may seem completely normal in the early stages of the illness, and there are no obvious alterations in the membrane's thickness [13].

- Stage 2: The capillary walls have started to thicken and have gathered a lot of epithelial cells, which are separated by extensions of GBM. These accumulations are not stained with the silver dyes approach, but the extension of GBM gives the impression that capillary is covered by saliences composed of type IV collagen and non-collagenous extracellular components [31].

- Stage 3: The deposits are surrounded by formed basement membrane, so capillary walls become thicker and lumens become narrower, and the basement membrane shows reduplicated on PAS stain.

- Stage 4: The basement membrane vacuolats, folds, and thickens, the deposit is no longer evident, capillary lumina are obliterated, and glomerular tufts show segmental or global sclerosis (**Figures 2** and **3**)

8.4.2 Immunofluorescence description

- In all stages of glomeruli, IgG4 staining may be seen in a subepithelial distribution, as shown in **Figure 4**.

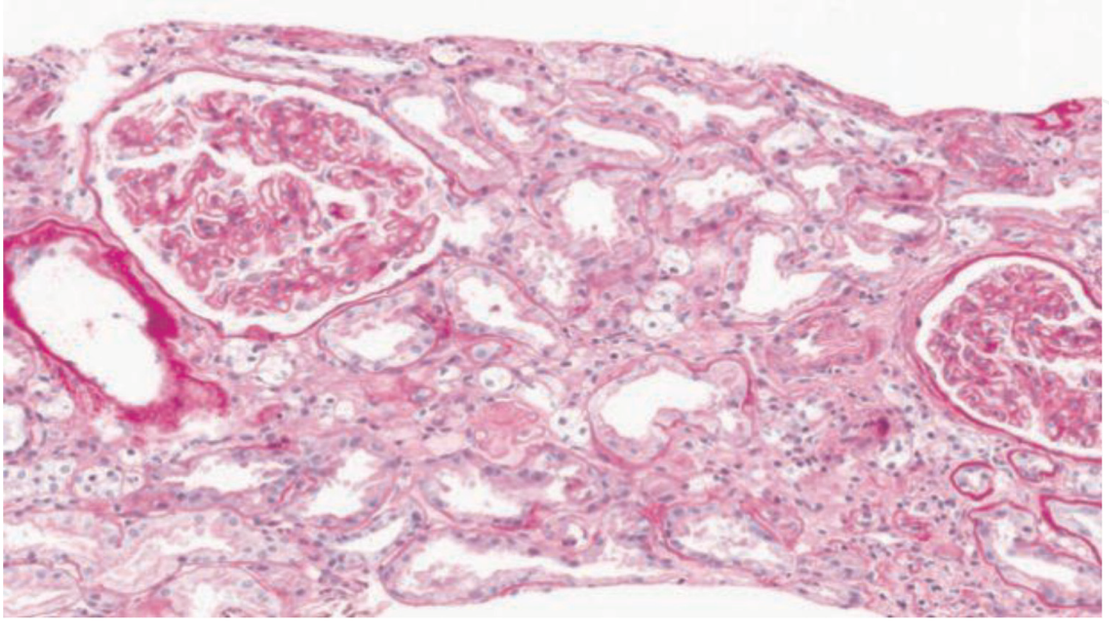

Figure 2.
PAS stain (100x) shows thickened glomerular basement membrane in a primary membranous nephropathy.

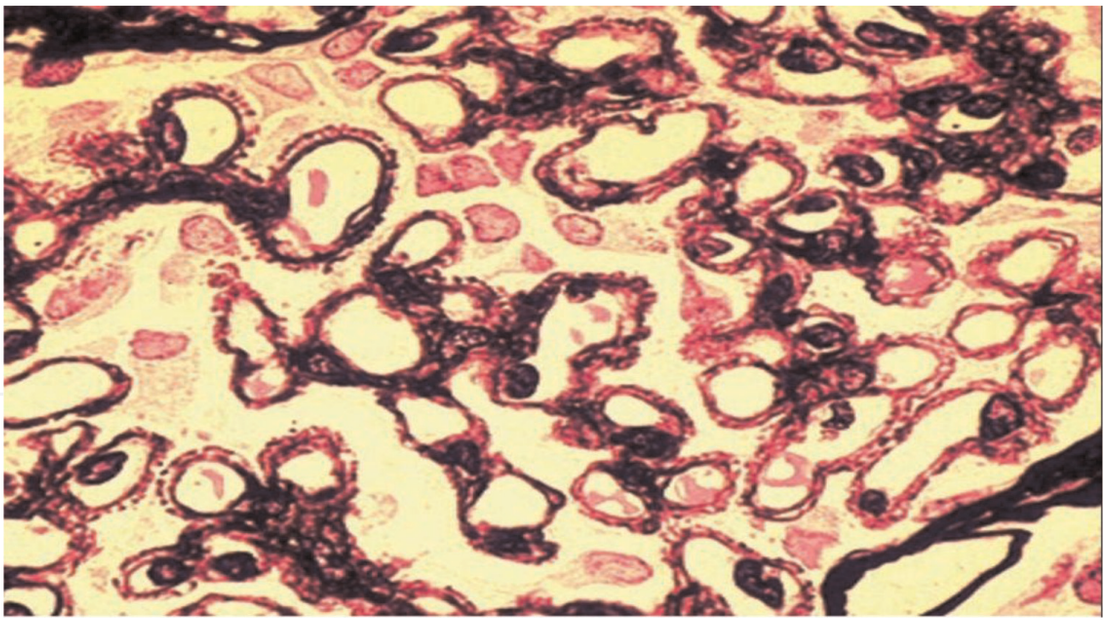

Figure 3.
Silver stain shows a pattern of subepithelial spikes of glomerular membrane basement in a primary membranous nephropathy [32].

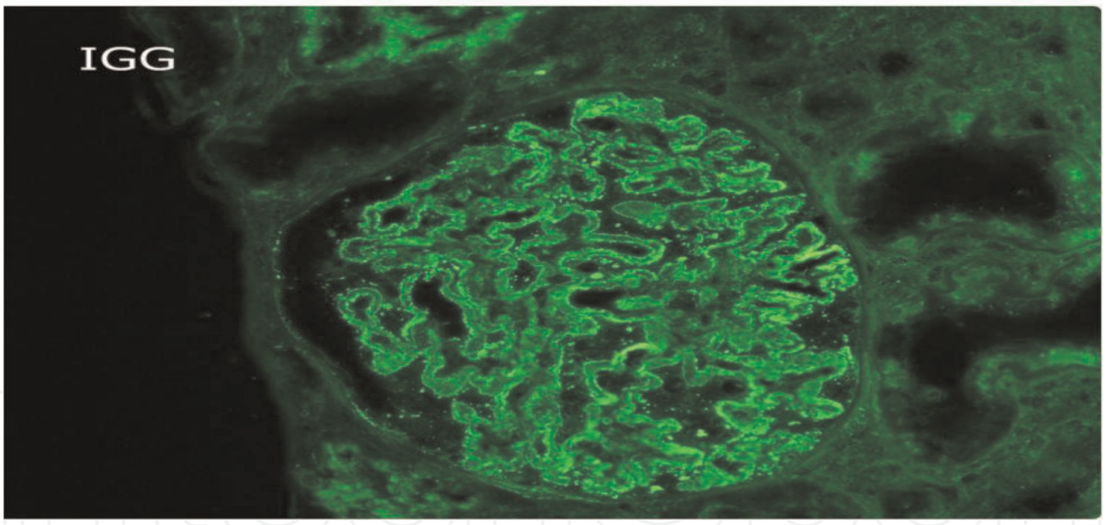

Figure 4.
Immunofluorescence microscopic examination for IgG under 400x power demonstrates a good diffuse granular staining along the capillaries of glomerular in a primary membranous nephropathy [17, 32].

8.4.3 Electron microscopy description

- Four stages of electron dense deposits' subepithelial localization are confirmed by electron microscopy, including:

    1. Scattered on the epithelial cells of the glomerular basement membrane

    2. Subepithelial deposits with dark silver staining with thickened basement membrane material as shown in **Figure 5**.

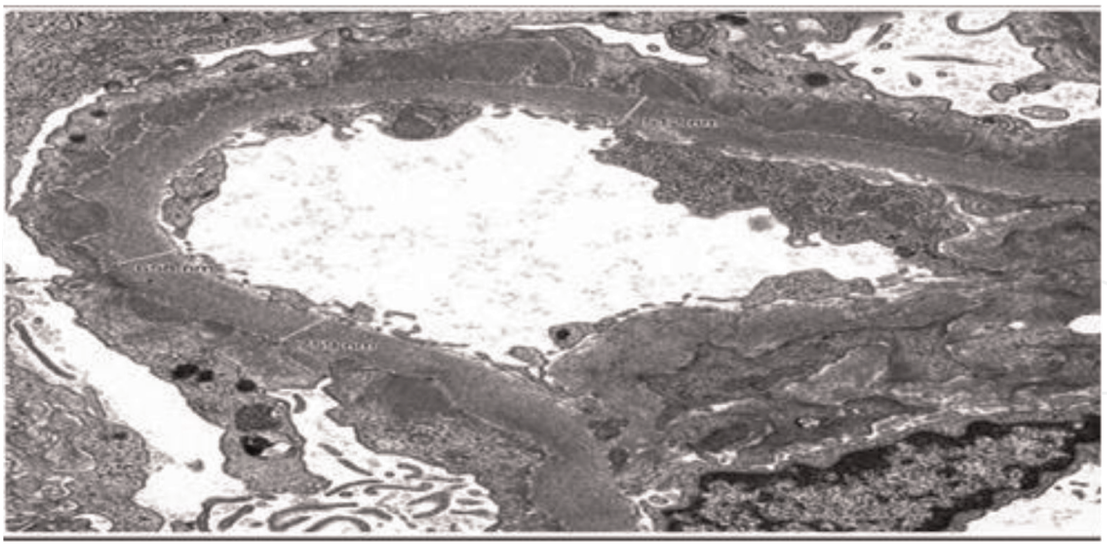

Figure 5.
Subepithelial deposits with thicker basement membrane material and dark silver staining [33].

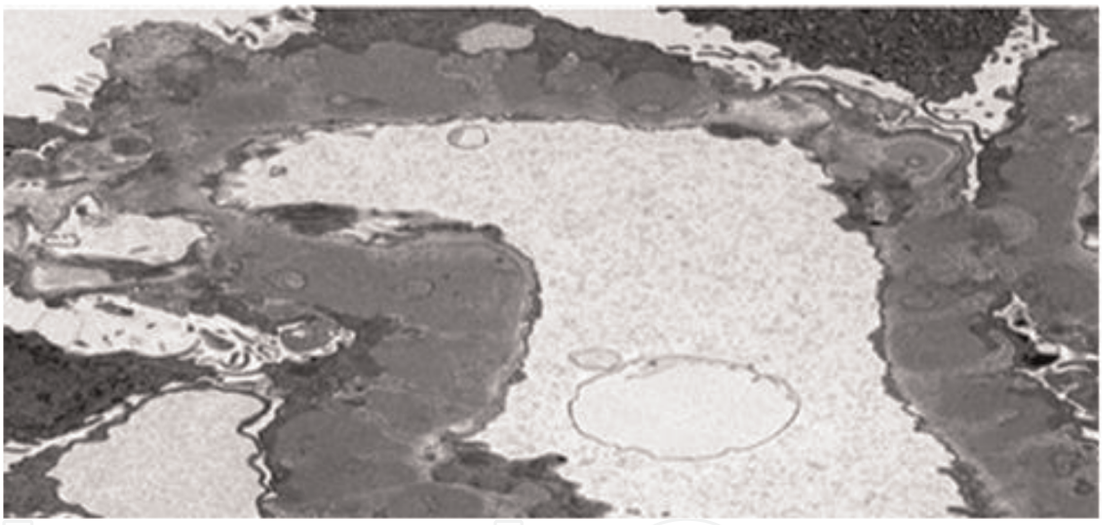

Figure 6.
Basement membrane material between and surrounding subepithelial deposits.

3. Basement membrane material between and surrounding subepithelial (or intramembranous) deposits as shown in **Figure 6**.

4. Areas that are electron-lucent are likely remnants of previous subepithelial immune complexes (**Figure 7**) [34].

8.5 New antibodies tests

Renal biopsy is frequently used to establish a new diagnosis of membranous nephropathy. The gold standard for analyzing and identifying the damage pattern of MN is renal biopsy. Standard light and electron microscopic investigation, however, was unable to capture the true nature of MN. When kidney tissue is examined histologically, immunological deposits can be seen along the glomerulus' basal membrane if the analysis is successful. Future diagnostics will greatly benefit from the

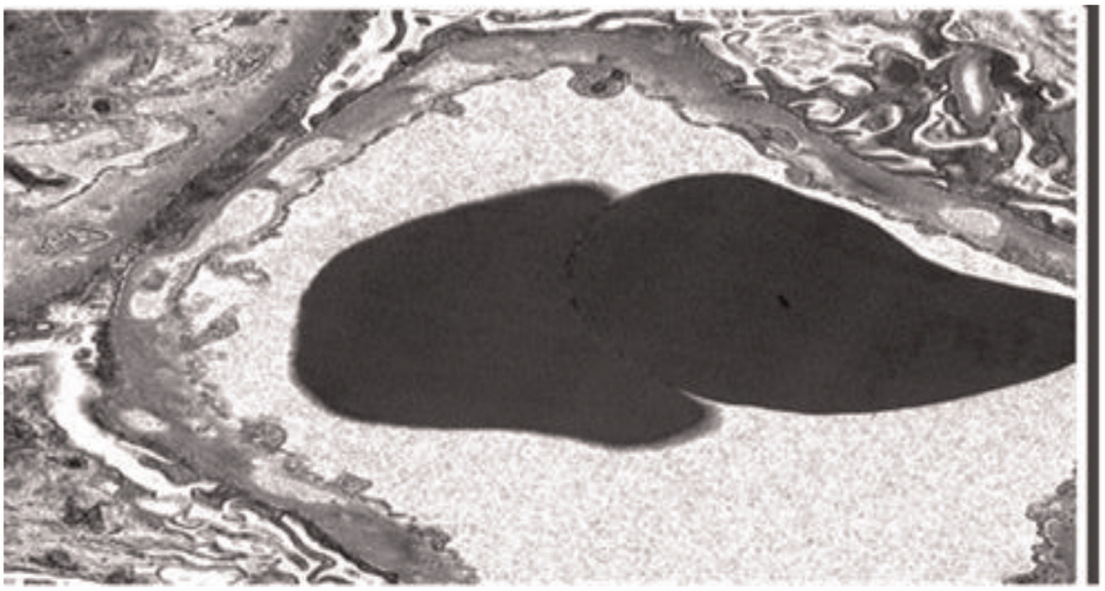

Figure 7.
Detailed foot process effacement and subepithelial immune complex deposits.

identification of the M-type antiphospholipase A2 receptor 1 (PLA2R) and antithrombospondin type 1 domain-containing 7A (THSD7A) antibodies as specific biomarkers for primary membranous nephropathy because it enables noninvasive diagnosis using straightforward serological testing.

8.5.1 Anti-PLA2R antibodies

In 2009, the M-type phospholipase A2 receptor (PLA2R) was discovered as the primary target in membranous nephropathy (MN). Anti-PLA2R antibodies have a high specificity and sensitivity of around 70–80% for primary membranous nephropathy (pMN) primary with various ethnic groups [35], but the prevalence of autoantibodies against PLA2R is unknown among Iraqi patients with MN [15]. Human podocytes express PLA2R, a 180-kDa transmembrane glycoprotein that is a member of the MR family of mannose receptors. Autoantibodies against M-type phospholipase A2 receptor (PLA2R) serve as specific diagnostic and tracking biomarkers for idiopathic membranous nephropathy (IMN), and their quantification helps monitor disease activity [36, 37]. The MN related to PLA2R defines patients with elevated levels of anti-PLA2R antibodies circulating in the serum as well as those with the presence of the PLA2R antigen in the kidney biopsy specimen stained with special staining. Patients with the presence of autoantigen but no autoantibodies account for approximately 10–15% of pMN cases. Iraqi study described a renal transplant patient with recurrent allograft membranous glomerulopathy who had a great rituximab response and outstanding graft function. Both the staining of the biopsies for the Ag of both PLA2.R and THSDA.7 and the serum testing for anti-PLA2R and anti-THSA7 were negative. IgG4 was confirmed by IgG subclass staining. He took two doses of rituximab once more and continued to respond quite well with no protein and normal renal function. Circulating anti-Ab of PLA2R1 is thought to be a particular biomarker of immunological activity in primary membranous nephropathy that correlates with indicators of disease activity (degree of proteinuria), and it is useful in predicting clinical outcomes like response to treatment and disease recurrence [9, 17, 38].

8.6 Anti-THSD7A antibodies

Thrombospondin type-I domain-containing 7A is a multi-domain transmembrane protein expressed on podocytes with molecular weight of 250 kDa [1, 39]. Its function is to increase the adhesion of cells. Therefore, anti-THSD7A antibodies lead to changes in the structure and function of the permeability of the slit diaphragm to plasma proteins. Scientific reports show a relationship between the THSD7A antigens and their antibodies with neoplasms [40]. They have linked proliferative conditions including rectal cancer, gallbladder cancer, or ALHE-angiolymphoid hyperplasia with eosinophilia with secondary MN related to the presence of anti-THSD7A as a result of the expression of THSD7A antigens within the tissues of some tumors. Allograft membranous glomerulopathy might be a recurring or de novo condition, according to an Iraqi study published in 2015. Since THSD7A antibodies seem to be uncommon in the serum of individuals with cancer-related membranous nephropathy, it was unlikely to have a diagnosis of malignancy-associated MN with 100% accuracy in this report [41, 42].

In pMN patients, autoantibodies against THSD7A are prevalent at a rate of 2.5 to 5%. This prevalence corresponded to 8–14% of the patients not having anti-PLA2R antibodies. It is noteworthy to notice that none of the individuals who tested positive for anti-THSD7A also tested negative for anti-PLA2R. Therefore, to identify a greater proportion of potential pMN patients, it is advantageous to preform simultaneous detection of anti-PLA2R and anti-THSD7A [20, 27].

THSD7A is expressed by some types of cancer, and many studies have been suggested that anti-THSD7A antibodies are associated with an increased risk of cancer-associated MN and screening for cancer was recommended in patients with anti-THSD7A positive MN. Anti-Ab of THSD7A can be present in primary MN patients and is not found in healthy people or people who have renal autoimmune disorders. The detection of PLA2R1 antibodies and anti-THSD7A antibodies enables the diagnosis of roughly 75–85% of cases, as PLA2R antibodies are present in about 70% of primary MN patients. Therefore, the simultaneous detection of anti-THSD7A and anti-PLA2R antibodies offers a comprehensive method for pMN detection [12, 21].

9. Response measurements

Improved kidney function, CR, and PR are the best recognized responses. CR is defined as a urine protein excretion of less than 0.3 g/24 hours together with normal serum albumin and creatinine levels. PR is defined as a urine protein excretion of less than 3.5 gram/day (24 hrs) together with improved or normalized serum albumin concentration and steady serum creatinine.

Following a CR, 30% or more of MN cases will relapse. However, most of them will return to subnephrotic level proteinuria and maintain acceptable long-term renal function. Clinical remission in patients with anti-PLA2R antibody positivity precedes a decline in circulating antibody titer, and a clinical resistance is linked to antibody persistence despite treatment.

9.1 Treatment

Patients can be provided with either nonimmune suppressive or immunosuppressive therapy based on the predicted criteria mentioned above.

In patients with MN, treating proteinuria with PR/CR is unmistakably related to a low rate of kidney disease development. There are potential newer markers like anti-PLA2R and THS D7A to distinguish between primary and secondary MN, predict prognosis, and evaluate therapy response [6].

9.2 Conventional treatment

This treatment includes managing edema, dietary protein intake, blood pressure, and hyperlipidemia. Loop diuretics are the cornerstone of treatment for edema control, along with a low-salt diet. It is typically advised to consume between 0.75 and 1.0 g of protein per kilogram each day. First-line antihypertensive medications should be antiprotein uric medicines such angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs). Treatment with an (ACEi) or an (ARBs) may be adequate to diminish concentration levels of proteinuria to a level of subnephritic in patients with low proteinuria levels of less than 4 grams per 24 hours, significantly reducing renal and cardiovascular risk. However, the use of these drugs alone is unlikely to result in a significant decrease in the level of proteinuria or the preservation of kidney function in individuals with greater levels of proteinuria.

About 7% of individuals with MN have severe nephrotic syndrome, and their risk of developing thromboembolic consequences is higher if their serum albumin level is lower than 2.8 g/dl. People with MN who are severely nephrotic (proteinuria >10 g/24 h and serum albumin 2.5 g/dl) should generally be considered for anticoagulation; prophylactic anticoagulation has been demonstrated to be more effective in nephrotic patients with range proteinuria.

9.3 Immunosuppressive agent therapy

It has been shown that a variety of immunosuppressive drug-based therapeutic modalities are effective in reducing the levels of proteinuria. According to the risk factor profiles, patients with MN can be categorized into three levels: low, medium, and high risk.

9.4 Treatment of those with a low risk factor

This group had a risk of developing kidney disease of less than 5% over a 5-year period following notification. Over a 6-month monitoring period, the patient at low risk had normal kidney function with a level of proteinuria less than 4 grams per 24-hour period. Therefore, a cautious course of treatment is effective for these patients.

9.5 Treatment of those with a moderate risk

This group still exhibits sustained daily excretion of urine protein at rates ranging from 4 to 8 g per 24 hours and intact renal function after 6 months of such therapy. Patients in this case utilized more than one of below approaches.

9.6 Corticosteroid immunotherapy

An early study was done on 72 patients with idiopathic nephrotic syndrome who took a course of high dose alternate day prednisolone for 2–3 months, and the results significantly reduced the progression to kidney failure, but this course had no effect

on the level of proteinuria. Hundred and fifty-eight patients with idiopathic MN were treated in a subsequent prospective randomized study for 6-month course of alternate prednisolone, and the results showed that corticosteroid therapy alone had no discernible benefits on either renal function preservation or remission induction after a mean of 45 months. Corticosteroid monotherapy has therefore been demonstrated to be ineffective in bringing about remission in MN patients [43].

9.7 Cyclosporine as an immunosuppressive drug

A high percentage of recurrence was found in early uncontrolled investigations using cyclosporine A (CSA), despite initial benefits being reported.

Thus, these drugs have been used for a long time for the maintenance in patients with CR or PR, particularly those at a high risk of recurrence. This must be balanced against the possibility of kidney damage from prolonged CSA exposure [29].

9.8 Treatment of patients at high risk

This patient category is characterized by persistently high proteinuria (28 g/day), highly elevated anti-PLA2R antibodies, or progressive kidney failure.

10. Corticosteroids

In the UK, a prospective double-blind randomized controlled experiment revealed no difference that was statistically significant between the control and treatment groups in the mean values of proteinuria and other kidney function markers like urea, creatinine, and uric acid.

Primary MN was treated with cytotoxic medications in conjunction with intravenous or oral corticosteroids [44]. Numerous research findings have shown how effective chlorambucil (leukeran) is at treating MN. Another trial randomly assigned participants to either supportive therapy only or a combination of prednisolone and leukeran. When compared to either the cyclosporine A (CSA) or supportive treatment groups, the prednisolone and chlorambucil group accrued the major end point, a further 20% fall in creatinine clearance, less frequently [29].

11. Cyclosporine

Renal functions and proteinuria significantly improved [45].

11.1 Mycophenolate mofetil (MMF)

Report by Miller and others found that treating 16 medium- or high-risk MN patients with MMF had no discernible effect on levels of creatinine or over the course of the experiment. An analysis of MN patients who had MMF treatment revealed similar results. Combined with steroids, three out of six patients' proteinuria improved by 61%.studies have shown that the majority of patients with primary glomerulopathies handled empirical MMF therapy well and were able to withdraw from steroids, ameliorate their nephrotic syndrome, and stabilize their renal function.

11.2 Rituximab

In different studies, the use of rituximab for patients with idiopathic MN showed more effective in both proteinuria and kidney function improvement [6, 46, 47].

11.3 Eculizumab

Eculizumab is a humanized anti-C5-monoclonal antibody designed to prevent the cleavage of C5 into its pro-inflammatory byproducts. More extensive research must be conducted in order to its involvement in the therapy of MN [48].

11.4 Adrenocortical tropic hormone

The use of synthetic adrenocorticotrophic hormone (ACTH) in the form of i.m injection in one study compared with combined corticosteroid and cyclophosphamide or chlorambucil showed no significant changes in the rate of remission (proteinuria/kidney function) [29].

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Conflicts of interest

The authors declare no conflict of interest.

Information about data availability

The authors will make the raw data used to support this article's conclusion available without undue reservation.

Nomenclature and abbreviations

ACEi	angiotensin-converting enzymes inhibitors
ACTH	adrenocorticotrophic hormone
ANA	antinuclear antibody
BSA	bovine serum albumin
CT	computed tomography
EBV	Epstein–Barr virus
FSGS	focal segmental glomerulosclerosis
GBR	glomerular basement membrane
MN	membranous nephropathy
NEP	Neutral endopeptidase

PLA2R	phospholipase A2 receptor
pMN	primary membranous nephropathy
SLE	systemic lupus erythematosus
THSD7A	anti-thrombospondin type 1 domain-containing 7A antibodies

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