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Progress in Integrative Traditional Chinese and Western Medicine Treatment of Idiopathic Membranous Nephropathy

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Abstract: ***MN is a major cause of nephrotic syndrome in middle-aged and elderly patients. However, relevant studies have shown that it has exhibited a significant trend of younger onset in China in recent years. Among different types of MN, IMN is the primary cause of primary nephrotic syndrome in adults. Nevertheless, IMN is characterized by unknown etiology, high recurrence rate, and poor prognosis. This article summarizes and explores the integrative treatment of membranous nephropathy with traditional Chinese medicine (TCM) and Western medicine, aiming to provide better support for clinical practice in the treatment of membranous nephropathy.***

Keywords: Idiopathic Membranous Nephropathy (IMN), Western Medicine, Traditional Chinese Medicine (TCM), Therapeutic Progress**.**

1. Introduction

Membranous nephropathy (MN) is a disease characterized by the deposition of immune complexes on the outer side of the glomerular basement membrane and beneath epithelial cells, accompanied by diffuse thickening of the basement membrane. It is the primary glomerular disease with the fastest-growing incidence in recent years [1], and also a major cause of nephrotic syndrome in middle-aged and elderly patients. However, relevant studies have shown that it has exhibited a significant trend of younger onset in China in recent years [1-2]. Among these cases, approximately 70-80% of patients have no clear cause for their disease, and thus are diagnosed with idiopathic membranous nephropathy (IMN)—the primary cause of primary nephrotic syndrome in adults. According to relevant data reports, 80% of patients with IMN mainly present with massive proteinuria, severe edema, hyperlipidemia, and hypoalbuminemia. IMN is characterized by unknown etiology, high recurrence rate, and poor prognosis. Statistics show that 40% of untreated IMN patients require renal replacement therapy (RRT) [3]. In terms of treatment, the primary goals are to slow the progression of the disease, reduce proteinuria excretion, protect the kidneys, and alleviate renal function damage. Western medicine commonly uses glucocorticoids and immunosuppressants; however, patients must bear the risks associated with these treatments, such as the occurrence of toxic and side effects including infection, metabolic disorders, osteoporosis, myelosuppression, and osteonecrosis of the femoral head. Additionally, immunosuppressive therapy has issues such as unstable efficacy, high recurrence rates, and nephrotoxicity of some drugs during use [4]. In recent years, with the continuous advancement of medical research, significant progress has been made in both Western medicine and Traditional Chinese Medicine (TCM) treatments for this disease. This article summarizes and explores the integrated TCM-Western medicine treatment of membranous nephropathy, aiming to provide better support for clinicians in the clinical management of membranous nephropathy.

2. TCM Clinical Research on IMN

TCM does not have a systematic discussion on the disease name of IMN. However, IMN patients often present with a series of clinical manifestations such as limb edema, massive proteinuria, and fatigue. Therefore, contemporary TCM scholars mostly classify IMN into the scope of TCM conditions like “Shuizhong” (edema), “Niaozhuo” (turbid urine), and “Xulao” (consumptive disease).

2.1 TCM Understanding of the Etiology and Pathogenesis of IMN

In TCM, the etiologies leading to chronic kidney diseases are mainly divided into two categories: external factors and internal factors. External factors mainly include the invasion of the six exogenous evils; internal factors mainly include congenital deficiency of constitutional endowment, improper diet or medication use, impairment caused by the seven emotions, and invasion of external pathogens.

Zhubing Yuanhou Lun (Treatise on Causes and Manifestations of Various Diseases) states: “All water diseases are caused by the deficiency of the spleen and kidney. “

Thus, the pathogenesis of IMN is mainly related to the dysfunction of the spleen and kidney. The spleen governs transportation and transformation, and it transports body fluids throughout the body through its transporting and transforming functions; the kidney governs water metabolism, and kidney Qi plays a crucial role in the production and excretion of urine. The two are closely connected, and the spleen and kidney cooperate to transport, distribute, and excrete body fluids in the human body. Therefore, most TCM practitioners believe that the pathogenesis of IMN takes the deficiency of the spleen and kidney—especially Qi deficiency of the spleen and kidney—as the root cause, and the obstruction of pathological factors such as wind, blood stasis,

and dampness as the secondary causes.

2.2 TCM Medication Treatment

2.2.1 Chinese Patent Medicine Treatment

1) Astragalus-Based Preparations

In clinical studies on idiopathic membranous nephropathy (IMN), the commonly used Chinese patent medicines with Astragalus membranaceus (Huangqi) as the principal herb (Jun Yao, the core ingredient in TCM prescriptions) are mainly Shenqi Granules and Sanqi Oral Liquid. Shenqi Granules: It contains 13 Chinese herbs including Astragalus membranaceus, and is a Chinese patent medicine developed by Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine specifically for the treatment of IMN. Sanqi Oral Liquid: Its main ingredients are Astragalus membranaceus and Panax notoginseng (Sanqi), and it is a Chinese patent medicine developed by Guangdong Provincial Hospital of Traditional Chinese Medicine [5]. A prospective randomized controlled study compared the efficacy and safety of the standard treatment (glucocorticoids combined with cyclophosphamide) and Shenqi Granules in treating IMN patients. After 48 weeks of group-based treatment, it was found that the degree of improvement in proteinuria and serum albumin was comparable between the two groups. However, the glomerular filtration rate (GFR) of patients in the Shenqi Granules treatment group was significantly increased, and adverse reactions were notably reduced [6]. Another study showed that intervention with Sanqi Oral Liquid significantly decreased the proteinuria level in passive Heymann nephritis (PHN) rats, as well as the deposition of IgG antibodies, complement C3, and membrane attack complex (MAC) in the body [7].

2) Rehmannia-Glutinosae-Based Chinese Patent Medicines

A commonly used Rehmannia-glutinosae-based Chinese patent medicine for treating IMN is Shenyan Kangfu Tablets. It is an empirical prescription developed by Mr. Zhao Enjian, a renowned TCM physician, with Rehmannia glutinosa (Dihuang) serving as the principal herb. An animal experiment showed that among the phenylethanoid glycosides extracted from Rehmannia glutinosa, verbascoside is the most crucial component. It can improve renal function in rats with nephritis through immune regulation [8].

3) Fermented Cordyceps Mycelium-Based Chinese Patent Medicines

Both Jinshuibao Capsules and Bailing Capsules are Chinese patent medicines made from fermented Cordyceps mycelium. Their main components include cordycepin, Cordyceps polysaccharides, ergosterol, amino acids, alcohols, protein polypeptides, and sphingolipids.

Studies have shown that cordycepin in fermented Cordyceps mycelium can reduce the infiltration of inflammatory cells, inhibit the deposition of immune complexes in the glomerular mesangial area, protect renal tissue, and delay the progression of renal dysfunction [9].

4) Abelmoschus Manihot Extract

Huangkui Capsules are a Chinese patent medicine prepared from the extract of dried corollas of Abelmoschus manihot (Huangshukui, Sunset Hibiscus). Their main active components include flavonoids, polysaccharides, tannins, and long-chain hydrocarbons, which exhibit potent anti-inflammatory and antioxidant effects.

Relevant studies have indicated that Abelmoschus manihot extract can inhibit the inflammatory response and reduce proteinuria by suppressing the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome and the p38 mitogen-activated protein kinase (p38MAPK) signaling pathway [10].

2.2.2 Self-Formulated TCM Prescriptions

Professor Zhang Farong holds that the syndrome type of “Yang deficiency of spleen and kidney with retention of water fluid and stasis blood” is extremely common among IMN patients. Based on the clinical manifestations and disease characteristics of patients with this syndrome type, and following the therapeutic principles of Zhang Zhongjing (a renowned TCM physician in the Han Dynasty), he created the Guiqi Zhenwu Decoction, which adheres to the principles of warming Yang, activating blood circulation, and promoting urination [11].

Professor Zhuang Kesheng argues that the occurrence and progression of IMN are attributed to “spleen-kidney deficiency and blood stasis in kidney”. In treatment, he prescribes medicines in accordance with the methods of “strengthening the spleen and tonifying the kidney, resolving stasis and dispelling dampness”, and has summarized his empirical prescription—Qiteng Tongluo Decoction. This prescription uses a large dose of Huangqi and multiple types of “vine herbs”. Huangqi targets the spleen for treatment, with the effects of invigorating Qi, activating blood; vine herbs dredging meridians and collaterals. Additionally, it is supplemented with herbs such as Baizhu and Baifuling to strengthen the spleen and dispel dampness, Chuanxiong and Danggui to nourish blood and resolve stasis, Buguzhi to tonify the kidney and replenish essence [12].

Professor Yuan Fang believes that “spleen-kidney deficiency” is the fundamental cause of IMN, while “wind, stasis blood, and dampness” are the secondary pathogenic factors, and the intertwinement of fundamental and secondary factors leads to the disease. Based on this underlying pathogenesis, she adopts the therapeutic methods of “strengthening the spleen and tonifying the kidney, activating blood to dredge” and has self-formulated the Jianpi Yishen Tongluo Decoction. In this prescription, Huangqi and Taizishen supplementing spleen and benefiting, which can significantly improve proteinuria symptoms; Shanzhuyu, Tusizi, and Niuxi supplementing kidney to consolidate essence [13].

Bao Xubo proposed the “spleen-kidney regulation method” for treating IMN, which involves acupuncture at specific acupoints: Guanyuan (CV4), Shenshu (BL23), Pishu (BL20), Sanyinjiao (SP6), and Zusanli (ST36). Studies have shown

that acupuncture at Shenshu, Guanyuan, and Zusanli not only promotes thermal metabolism in the lumbosacral region and relieves low back pain but also regulates blood lipid levels, reduces glomerular capillary pressure, decreases proteinuria, and improves renal function [14].

Moxibustion, a traditional TCM therapy, has the effects of tonifying deficiency, unblocking collaterals, promoting Qi circulation, and dissipating blood stasis, and often achieves favorable therapeutic effects in treating chronic diseases. Its mechanism lies in applying thermal stimulation to specific acupoints of the human body through the combustion of mugwort leaves, which promotes the circulation of Qi and blood in the body to achieve the purpose of treating diseases. Mao Jingyu found that after moxibustion at Shenshu, Pishu, Guanyuan, Zusanli, and Sanyinjiao, the total score of TCM syndrome in the observation group was lower than that in the control group; the 24-hour urinary protein (24h UTP) and blood lipid levels of patients in both groups decreased compared with those before treatment, and the observation group had lower levels than the control group; the serum albumin levels of patients in both groups increased compared with those before treatment, indicating that the treatment was effective [15].

After searching the ancient TCM literature database, Chen Yin found that there are five main external TCM therapies for treating renal edema: external application, external washing, fumigation, foot bathing, and moxibustion, among which external application is the most commonly used [16]. External application usually utilizes the properties of drugs themselves to guide the dispersion of external pathogens through medicinal effects—often using aromatic resuscitation - inducing drugs, potent water-expelling drugs for eliminating stagnation, or leveraging the warm nature of the therapy to warm and unblock collaterals, promote blood circulation, assist medicinal effects in dredging external pathogens, and improve edema. Meanwhile, by comparing the efficacy and safety indicators of two groups of patients treated with external application of buckwheat packs, it was found that external application of buckwheat packs could significantly improve the state of renal edema in patients.

3. Clinical Research on IMN in Western Medicine

3.1 Etiology and Pathogenesis in Western Medicine

The pathophysiological mechanism of IMN has not been fully elucidated, but the interaction of multiple factors (such as genetics, environment, autoimmunity, antigen type, and the physical and chemical properties of related proteins/structures) is a necessary condition for the development of the disease.

3.1.1 Immune Pattern of Autoantigens

IMN dominated by different autoantigens may have distinct exposure and immune pathways—for example, the differential release modes of secretory and transmembrane autoantigens. However, patients with the same autoantigen may also exhibit different immune recognition pathways [17]. Autoantigens can be exposed to the immune system through conformational changes of epitopes and release of new epitopes, molecular mimicry, and non-specific immune activation by inflammation. Most autoantigens in IMN are B-cell epitopes and associated with protein conformation; for instance, anti-SEMA3B antibodies can recognize cryptic epitopes exposed by the disruption of disulfide bonds. Molecular mimicry, on the other hand, triggers autoimmune responses through the similarity between exogenous peptides and self-peptides [18]. For example, the identification of anti-PLA2R antibodies confirms that IMN is an autoimmune glomerular disease. The application of immunosuppressive agents has fundamentally changed the therapeutic direction of IMN. The 2021 KDIGO Guidelines recommend anti-PLA2R antibodies as biomarkers for remission and prognosis in IMN patients.

3.1.2 Genetic Factors

Genetic factors render individuals susceptible to environmental triggers of renal autoimmunity. Exposure to environmental infectious agents may be modified by epigenetic factors, which activate the innate immune system through interactions with Toll-like receptors (TLRs) and complement, leading to MN. Genome-wide association studies (GWAS) have identified that single nucleotide polymorphisms (SNPs) in genes such as PLA2R1, HLA, and immune/inflammation-related genes (NFKB1 and IRF4) are closely associated with IMN, with ethnic specificity: DRB1*1501 is associated with East Asians, DQA1*0501 with Europeans, and DRB1*0301 is a risk allele in both ethnic groups [19]. The team led by Academician Liu Zhihong sequenced the entire major histocompatibility complex (MHC) region in DNA samples from 99 PLA2R-associated IMN patients, 50 PLA2R-unrelated MN patients, and 100 healthy controls [20]. The study found that HLA-DRB1*15:01 was present in 81. 8% of PLA2R-associated MN patients and 21% of healthy controls, while HLA-DRB3*02:02 was present in 60. 6% of PLA2R-associated MN patients and 28% of healthy controls. These two HLA risk alleles (HLA-DRB1*15:01 and HLA-DRB3*02:02) are independently and strongly associated with an increased risk of developing PLA2R-associated MN. Currently, multiple gene loci have been confirmed to be potentially associated with IMN pathogenesis both domestically and internationally; knocking down the expression of corresponding risk genes may be a future approach for IMN intervention.

3.1.3 Environmental Factors

Environmental stimuli can also induce IMN. For example, air pollution contributes to IMN pathogenesis by inducing pulmonary inflammation and oxidative stress. PM2. 5 may trigger the production of anti-PLA2R antibodies in the lungs; these antibodies then enter the kidneys via the bloodstream, causing renal immune damage. Additionally, PM2. 5 can activate antigen-presenting cells (APCs) and autoreactive T cells in the inflammatory microenvironment, which further induce humoral immune responses against extrarenal autoantigens, ultimately leading to the development and progression of IMN [21].

3.1.4 Immune Regulation Disorders

IMN is characterized by a significant imbalance in T-cell

subsets, mainly manifested by increased ratios of Th2/Th1, Th17/Treg, and Tfh/Tfr cells. Th2 cells secrete IL-4 and IL-5 to promote humoral immune responses, while Th17 cells secrete IL-17a to mediate neutrophil involvement in pro-inflammatory responses. Secondly, in IMN, the proportion of Treg cells is reduced and their suppressive capacity is impaired, leading to a decrease in anti-inflammatory factors such as IL-35 and an increase in pro-inflammatory factors, which exacerbate renal lesions [22]. B-cell responses are characterized by a significant upregulation of circulating plasma cells and regulatory B cells in IMN, which may explain the persistence of circulating antibodies and is likely closely associated with B-cell activating factor (BAFF).

3.1.5 Antibodies and Complement

Antigen-associated IMN is driven by different types of antibodies (IgG4/IgG1) to trigger autoimmunity. In the early stage of pathogenesis, small amounts of IgM and IgG3 are deposited in the glomeruli; subsequently, IgG1 becomes the main subtype for antigen clearance. Persistent antigen stimulation eventually induces the production of high-affinity IgG4, which exerts anti-inflammatory effects by inhibiting the binding of other IgG subtypes to antigens. However, the high affinity of IgG4 also impairs podocyte function [23].

Complement activation is another key factor contributing to the pathological damage of IMN: immune complexes formed by podocyte in-situ antigens and circulating autoantibodies are deposited subepithelially on podocytes, which then activate the complement system and form membrane attack complexes (MACs), leading to podocyte damage and the development of IMN. Different antibodies in IMN may activate different complement pathways: the classical and lectin pathways are usually immunologically triggered, while the alternative pathway is continuously activated at a low level [24]. Studies have shown that in PLA2R-positive patients, the complement activation pathway may be dominated by the lectin pathway. Therefore, antigens such as HTRA1, NTNG1, and CNTN1— which are dominated by IgG4—may exhibit a complement activation mechanism similar to that of PLA2R-associated IMN [24].

3.2 Western Medicine Treatment

3.2.1 Symptomatic Treatment

Basic treatment is formulated with reference to guidelines such as the 2021 KDIGO Clinical Practice Guidelines for Glomerular Diseases and the Expert Consensus on Protein Nutritional Therapy for Chronic Kidney Disease [25-26]. Since IMN patients mainly present with massive proteinuria, severe edema, hyperlipidemia, and hypoalbuminemia, dietary management should include supplementary high-quality protein; however, to avoid increasing renal burden, the daily intake of high-quality protein is optimally 0. 8–1. 0 g/kg, with adequate caloric intake maintained at 30–35 kcal/(kg·d).

Diuretics are the first-line choice for eliminating or improving edema and are classified into three categories: thiazide diuretics, loop diuretics, and potassium-sparing diuretics. Furosemide is the most commonly used diuretic in clinical practice. For severe edema, strict restriction of fluid and sodium intake is necessary to prevent fluid-sodium retention and further exacerbation of edema: sodium intake should be <6 g/d for patients with edema, and <2 g/d for those with severe edema. Additionally, albumin supplementation and renal replacement therapy are important approaches for edema resolution.

Hyperlipidemia damages multiple target organs such as the heart and kidneys; hypercholesterolemia can reduce glomerular filtration rate (GFR) and promote glomerulosclerosis. Therefore, statins are commonly used clinically for lipid regulation. Due to the imbalance between the coagulation and fibrinolytic systems, coupled with long-term use of diuretics and hormones, IMN patients are in a hypercoagulable state, which often leads to thrombosis and embolism. The 2021 KDIGO Guidelines recommend initiating prophylactic anticoagulation when serum albumin levels are below 25 g/L. Low-molecular-weight heparin (LMWH) or oral anticoagulants are clinically used to safely and effectively reduce the risk of thrombotic events in MN patients.

3.2.2 Immunotherapy

1) Glucocorticoids

Glucocorticoids (GCS) exhibit anti-inflammatory, immunosuppressive, and proteinuria-reducing effects, and are widely used in the field of nephrology. Clinically, GCS are often combined with other immunosuppressants. Compared with the severe complications of long-term high-dose GCS use (such as osteoporosis, infection, glucose metabolism disorders, and peptic ulcers), low-dose GCS have higher safety and are suitable for patients with poor physical status, such as the elderly and children.

2) Alkylating Agents

Alkylating agents are cytotoxic drugs; currently, the commonly used alkylating agents for IMN are chlorambucil and cyclophosphamide. Clinically, these agents have proven efficacy in treating IMN: they can induce long-term remission of nephrotic syndrome, reduce proteinuria, and protect renal function. In particular, the combination of glucocorticoids and cyclophosphamide has a lower recurrence rate, fewer adverse reactions, and higher tolerance [27]. However, while providing significant clinical benefits, their potential severe side effects cannot be ignored, such as myelosuppression, gastrointestinal reactions (nausea, vomiting, etc.), and abnormalities in blood pressure and blood glucose.

3) Calcineurin Inhibitors (CNIs）

The application scope of calcineurin inhibitors (CNIs） in immune system diseases has been expanding; in recent years, they have become the main therapeutic drugs for refractory nephrotic syndrome. CNIs include cyclosporine A and tacrolimus. In recent years, with the reporting of cases of toxic effects induced by cyclosporine A (such as hirsutism, gingival hyperplasia, hepatotoxicity, nephrotoxicity, and sudden blindness), tacrolimus— which has better safety and stronger immunosuppressive effects—is often preferred clinically for

IMN treatment. Clinical studies have confirmed that the combination of glucocorticoids and tacrolimus in IMN patients can effectively improve blood lipid and proteinuria levels, reduce inflammatory responses, protect renal function, and exhibit good medication safety [28].

4) Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is a 2-ethyl ester derivative of mycophenolic acid and a new generation of clinical immunosuppressants. Initially used in the field of organ transplantation, it is now also commonly used to treat various glomerular diseases. Relevant studies have shown that in clinical observations of IMN, the efficacy of the GCS + MMF regimen is comparable to that of the GCS + cyclophosphamide regimen in reducing proteinuria, increasing serum albumin, lowering blood lipids, and improving renal function. However, the GCS + MMF regimen has a significantly higher total effective rate and fewer adverse reactions [29].

5) Rituximab (RTX)

Rituximab damages B cells through mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC) and direct induction of apoptosis; it also reduces proteinuria by decreasing immune complex deposition, ultimately exerting therapeutic effects. The use of biological agents for treating immune glomerular diseases represents a major advancement in nephrology, providing more therapeutic options for IMN patients [30]. RTX has currently become a first-line treatment for patients with moderate-to-high-risk MN and refractory MN. However, relevant literature reports indicate that some patients may experience B-cell reconstitution, rebound of serum anti-PLA2R antibodies, increased proteinuria, and elevated serum creatinine (SCr) after RTX use.

6) Obinutuzumab (OBZ)

Obinutuzumab is a novel humanized anti-CD20 monoclonal antibody with higher affinity for the CD20 molecule. OBZ clears B cells completely and for a longer duration, but the risk of infection is a major concern in clinical application [31]. Relevant experiments have shown that its B-cell depletion effect is more significant than that of RTX; however, pharmacokinetic evidence for its use in treating immune diseases is still lacking [32]. In recent years, with multiple literature reports indicating an overall effective rate of >80% for OBZ in the treatment of refractory or recurrent MN [33-34], OBZ has gradually demonstrated efficacy in IMN treatment, but its safety still requires more clinical research [35].

4. Summary and Discussion

MN is currently showing a trend of younger onset. Among MN cases, IMN is the primary cause of primary nephrotic syndrome in adults, accounting for 70%–80% of all membranous nephropathy cases. It is characterized by the “three highs and one low” presentation (massive proteinuria, severe edema, hyperlipidemia, and hypoalbuminemia), along with a high recurrence rate and poor prognosis, and has exhibited a trend of younger onset in recent years.

From the perspective of TCM, the pathogenesis of IMN is rooted in spleen-kidney deficiency and involves wind, blood stasis, and dampness. TCM treatments for IMN include Chinese patent medicines, self-formulated prescriptions, and external therapies, all of which have achieved favorable therapeutic effects.

In Western medicine, IMN is believed to be triggered by multiple factors such as genetics, environment, and immune disorders. Its treatment mainly focuses on symptomatic management and immunotherapy. In recent years, besides the conventional therapy of glucocorticoids combined with immunosuppressants, monoclonal antibody drugs—primarily RTX and OBZ—have also demonstrated good efficacy in the treatment of membranous nephropathy.

The authors believe that with the continuous advancement of medical science, more drugs with better therapeutic effects and fewer toxic side effects will be applied in the clinical treatment of membranous nephropathy.

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