

Progress in the treatment of lupus nephritis with Chinese medicine

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Abstract: By examining the recent domestic and international literature, we provide a breakdown of Chinese medicine in the treatment of lupus nephritis in recent years. It summarizes the etiology and pathogenesis of the disease, the historical theoretical sources of TCM evidence-based treatment and the composition of prescriptions and medicines, elaborates on TCM stage-based treatment, and outlines various TCM characteristic treatment methods including internal herbal tonics, acupuncture, medicinal baths, tui-na and enemas. The results showed that the above-mentioned TCM treatment methods not only have precise clinical efficacy, but also can appropriately reduce the frequency of hormone use, thus alleviating the physical harm caused by the related side effects, with considerable safety and effective relief of patients' pain.

Keywords: Lupus nephritis; Hormone; Chinese medicine treatment; Research progress

1. Introduction

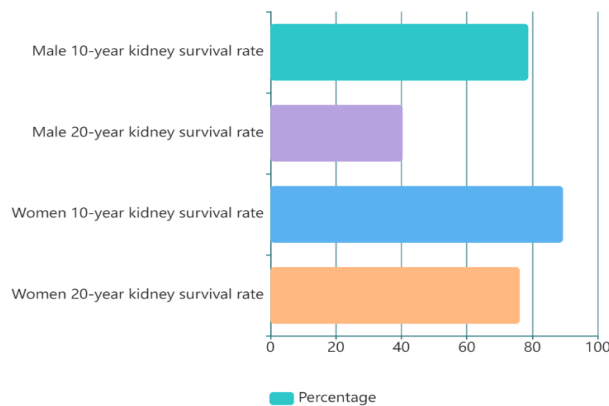


Figure 1: Renal survival rate by gender

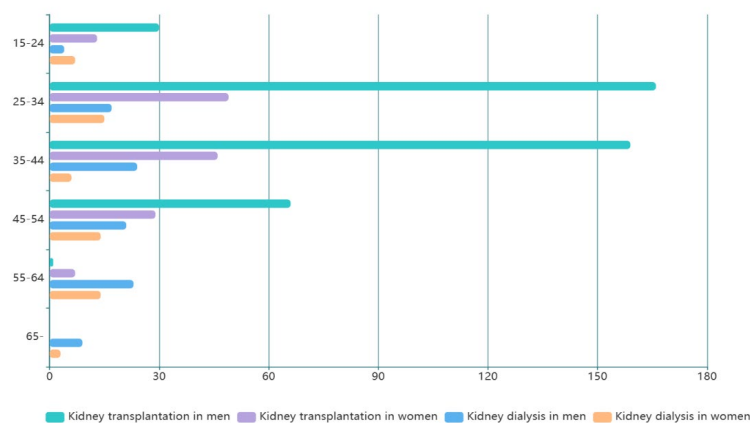


Figure 2: Prognosis of kidney disease by age group

Systemic lupus erythematosus (SLE) is an autoimmune disease with multisystem damage as a common manifestation. Lupus Nephritis (LN) is a common complication of SLE. It is also a secondary nephritis disease. 35-60% of patients with SLE usually develop renal involvement early in the course of the disease [1]. The disease is more common in women of childbearing age and is easily overlooked, the disease is usually progressive, only a few patients the first onset of chronic kidney failure [2]. Approximately 5-20% of patients with diagnosed LN will progress to end-stage renal disease within 10 years, which places a great burden on patients [3], see Figures 1, 2. Thus, early treatment has a particular impact on the survival of LN patients. Most researchers now believe that the pathogenesis of LN is related to immune complex deposition, complement system abnormalities, immune cell abnormalities, cytokine changes and gene regulation abnormalities [4]. Therefore, Western medicine mostly adopts various hormones, biological agents and immunosuppressive drugs for treatment, which are fast-acting and effective, but have a high relapse rate and obvious toxic side effects when applied continuously, and can produce many complications such as hypertension, hyperlipidemia, femoral head necrosis and liver and kidney function damage, see Figure 3. No LN-related disease name is recorded in Chinese medicine, but according to its clinical manifestations, LN can be classified as Chinese medicine "edema", "yin-yang toxicity", "kidney wind toxicity", "blood wind sore", and "horse cherry dan" and other ranges [5]. The basic pathogenesis is based on liver and kidney yin deficiency, with heat toxicity and blood stasis as the symptoms. Treatment relies on unique theoretical guidance, evidence-based treatment, and individualized formulation of treatment plans, add and subtract with the evidence, significantly reduce the adverse reactions, maintain the residual kidney function, while increasing the effectiveness and reducing toxicity. Based on extensive reading of the literature, the author describes the TCM treatment of LN as follows.

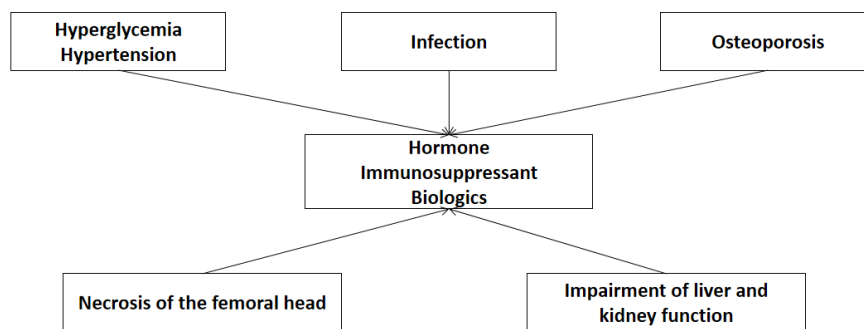


Figure 3: Hormone, immunosuppressant and biological agent use related

2. Etiology and pathogenesis

Western medicine generally believes that LN is caused by immune damage to the kidneys and inflammation caused by the accumulation of immune complexes in the blood, which can lead to renal interstitial fibrosis in the later stage. According to the basic theory of Chinese medicine, deficiency of essence deficiency is the internal basis of LN disease and the external condition is the evil of six pestilences. Therefore, LN is a deficiency of the essence in the kidney, which is present throughout the disease, together with dampness, heat, and evil toxins, resulting in a lingering disease that is difficult to cure. According to the Jin Kao Yao, "Yang toxin is a disease body pain like a staff", which indicates that LN is caused by fever and other symptoms due to heat toxin accumulation. Kuang Tang Hong et al. [6] believed that the onset of LN is based on the deficiency of kidney yin, and the evil toxin is an important factor in the onset of the disease, and its condition is complex and multifaceted. Zhu Yueling [7] Seventy-three clinical cases of LN patients were selected, and the information of patients was collected on day 7, 3 months, and 2 years in sequence using the method of longitudinal study, and the cases were typed according to the four diagnostic data. After the statistics, it was concluded that LN is mostly characterized by the incandescent type of heat and toxicity, and the disease process is commonly characterized by stasis-heat paralysis, spleen-kidney-yang deficiency and wind-damp-heat paralysis. Ou Linyan and Wu Jinyu et al. [8] concluded that the pathogenesis of LN is based on the deficiency of spleen and kidney, on the basis of which external heat and toxicity, dampness and turbidity are the causes, and in the remission period, liver and kidney yin deficiency is the most common. Yingying Deng and Shuifu Tang et al. [9] believed that LN had a long course and complicated pathogenesis, Kidney-Yin deficiency is the main cause, while turbid toxin and blood stasis are the

symptoms; heat toxin and blood stasis are common in the acute stage, while Spleen-Kidney-Yang deficiency is the main cause in the remission stage.

3. Chinese medicine treatment

3.1. Identification and treatment

One of the characteristics of TCM is the diagnosis and treatment of diseases, doctors can analyze the four diagnostic data of patients and develop unique plans for patients. By reviewing a large number of recent literatures, it is concluded that heat toxicity, liver and kidney yin deficiency, yin deficiency internal heat, and spleen and kidney yang deficiency are common subtypes of LN patients, see Table 1. Most of the treatment principles are to clear heat and detoxify, nourish the liver and kidney, nourish yin and clear heat, and strengthen the spleen and kidney to achieve the treatment goal of harmonizing qi and blood and regulating yin and yang, then the spirit will be toned and the disease will be gradually removed.

Table 1: TCM evidence-based treatment

TCM certificate type	Main manifestations	The law of treatment
Heat is poisonous	High fever, spots, red tongue, fast pulse	Detoxify heat
Liver and kidney yin deficiency	Low temperature in the afternoon, facial erythem, upset and sleepless, red tongue and less moss, fine pulse count	Nourishes liver and kidneys
Yin deficiency and internal heat	Low-grade fever in the afternoon, night sweats, sore waist and knees, facial macules, red tongue and less lichen, and fine pulse count	Nourish the yin and clear the heat
Spleen and kidney yang deficiency	Both lower extremities and even systemic edema	Strengthens the spleen and tonifies the kidneys

3.1.1. Thermal detoxification to dispel erythema

In the "Collection of Medical Formulas", it is said that "blood heat does not dissipate, steaming in the skin is spotted, light as a rash, heavy as Jinwen", because heat is depressed in the internal forced blood and spotted on the outside. In the early stage of LN, the Blood is burned by heat and toxins, resulting in strong heat, spots, red and vivid tongue, and counted pulse, so the treatment is to clear heat and cool the Blood. Wang Fan-sheng^[10] collected 90 patients with systemic lupus erythematosus with excessive heat and toxin and randomly divided them into two groups. The control group was only given prednisone (produced by Sichuan Kangteneng Pharmaceutical Co., LTD., 20-40mg/ day, and the dose was adjusted according to the condition), and the experimental group was given Rhizoma Dihuang Tang on this basis, after 12 weeks of treatment, the IgG and anti-dsDNA of the experimental group were lower than those of the control group; the mental status score and overall effective rate were higher than those of the control group, while the improvement of symptoms and the time spent in hospital were shorter than those of the control group, indicating that Rhizoma Dihuang Tang, which has the ability to clear heat and detoxify toxins, cool blood and disperse blood stasis, and is mild and safe, can effectively control the further development of the disease. It indicates that Rhizoma Dihuang Tang, which has the ability to clear heat and detoxify toxins, cool blood and disperse blood stasis, and is mild and safe, can effectively control the further development of the disease and improve the corresponding symptoms. He Hao^[11] included 106 SLE patients divided into 2 groups, the control group was treated with prednisone tablets (0.5-1 mg/kg-1, dose adjusted according to the condition) and azathioprine (0.1 g/1 time/day, produced by Zhejiang Otocon Pharmaceutical Group Co., Ltd.), while the patients in the observation group were treated with Artemisia fuzheng detoxification soup (20 g each of Artemisia annua, Banlangen and Huangqi, and 20 g each of Radix Astragali) on top of the control group. After 2 months, the immunoglobulin values of patients in both groups were significantly reduced, the degree of decrease in serum ds-DNA titer in the observation group was significant compared with that in the control group, the Chinese medicine evidence points such as fever and rash in the observation group were significantly reduced compared with those before treatment, and the total effective rate in the observation group was significantly higher than that in the hormone group, which has the ability to remove fire and detoxify toxins, clear dampness and heat, and dispel evil and help righteousness, can significantly repair the immune system of SLE patients, effectively inhibit the production of inflammatory factors, and adjust the balance of yin and yang while also reducing the

adverse effects brought about by immunosuppressive drugs.

3.1.2. Nourishing Yin and clearing heat and toxin rash

The Feng's Secret Book of the Jinan: "hair spot, Yang Ming by the lord inflammation of the poison is also caused. However, there are two symptoms, Yang toxicity hair spot like Yin toxicity hair spot, must be no great heat gathered in the stomach, smoked in the lungs, transmitted to the skin and for the spot also", clinically this evidence is manifested in the afternoon low fever, facial erythema, disturbed heart less sleep, tongue red with little coating, and a fine pulse. Wan Liwei^[12] eighty patients with yin deficiency and internal heat type SLE were included and randomly divided into 2 groups, the control group was treated with hydroxychloroquine sulfate (0.1g/2 times/day) combined with prednisolone acetate tablets (40mg/1 time/day). The treatment group was combined with Artemisia turtle shell soup (30g each of white flower and snake tongue grass, raw earth and earthwort, 20g each of Danpi, XuanShen and MoHaoLian, 15g each of ground bone bark, YinChaiHu, Artemisia, turtle shell, BaiWei, Lady's mantle and ZhiMu), IFN- γ and Th1/Th2 levels in the treatment group were significantly higher in the control group, and IL-4 levels were lower than in the control group, while the treatment group had significantly fewer adverse events during the course of treatment compared to the control group. Zhang Minjun and Zhang Panpan et al.^[13] treated 46 patients with yin deficiency and internal heat and water-stasis interconnection type of LN with cyclophosphamide in combination with kidney tonifying and yin nourishing soup (21 g each of elderberry, raw earth, Centella asiatica, cat's claw and Salvia miltiorrhiza) on the basis of basic symptomatic treatment, and the control group was treated with static cyclophosphamide (produced by Shengdi Pharmaceutical Co., Ltd, 0.6 g/time/week for two weeks and then reapplied at an interval of one week) for 6 months of intervention. The total effective rates were 93.48% and 77.78% in the kidney tonifying and yin nourishing soup group and cyclophosphamide group, respectively. Zhong Zhao and Bryan Hong^[14] eighty cases of SLE patients with Yin deficiency and internal heat were selected and randomly grouped, forty patients in the treatment group were treated with self-formulated yin-deficiency and heat-relief soup (30g each of Artemisia annua and Serpent's tongue grass, 20g of Radix Rehmanniae Sinensis, 15g each of turtle nail (roasted), fried dandruff, and yam, 10g each of cow's knee and ground bone bark, and 6g of fried licorice) combined with conventional western medicine, The control group used prednisone acetate tablets (produced by Zhejiang Xianju Pharmaceutical Co., Ltd., 5-20mg/dose, 1 time daily)+ Hydroxychloroquine sulfate tablets (0.1g/dose, 2 times a day, manufactured by Shanghai ShangPharma Central & Western Pharmaceutical Co.), after 12 weeks of intervention, the results showed that Zhiyin Draining Heat Soup could significantly reduce SLEDAI scores and effectively improve SLE symptoms.

3.1.3. Tonifying the kidneys and nourishing the liver and retreating the symptoms

In SLE patients, deficiency in the kidneys leads to loss of all the remaining organs, and stasis of blood is generated when the Qi and blood are not smooth. This evidence is clinically manifested by low fever in the afternoon, night sweats, and facial rash. He Hao^[15] used tonifying kidney and marrow sealing soup (30g each of Radix Rehmanniae and Herba Cistanches, 15g of Huai Shan, 10g each of Radix Achyrantes Bidentatae, Phellodendron Bidentatae and Glycyrrhiza Glabra, 6g of Sharen) combined with Leflunomide (50mg/d for the first 3 days, gradually adjusted to 20mg/d) to treat 57 SLE patients with liver and kidney yin deficiency, while the control group was treated with Leflunomide alone. After continuous treatment for 3 months, the total effective rate of the observation group (96.49%) was better than that of the control group (85.96%), suggesting that the combination of Kidney and Marrow Tonic soup with Leflunomide was clinically effective in treating patients with SLE (liver and kidney yin deficiency), which could promote faster recovery of SLE patients, reduce the side effects of Leflunomide alone, and achieve enhanced efficacy. Liu Zhi et al^[16] used a self-developed formula for tonifying the kidney and detoxifying the liver (15g each of Radix et Rhizoma Dioscoreae, Semen Cuscutae, Peony Bark, Fructus Lycii, Zhi Mu and Radix Paeoniae, 20g each of Jinyin Hua and Yam, 12g each of Cornu Cervi Pantotrichum and Chuan Shao, 10g of Safflower and 6g of Glycyrrhiza glabra) in combination with glucocorticoids (40-60mg/day of prednisone or 5-15mg/day of dexamethasone in early full doses, gradually reduced to a maintenance dose after the disease stabilized. After 3 months of continuous intervention, immunoglobulin and urine protein quantification were significantly lower in the treatment group than in the control group, and Hb, WBC, PLT, serum TNF- α and IL-8 were significantly higher in the treatment group than in the control group. In conclusion, the self-prepared formula for tonifying the kidney and detoxifying the liver is effective in treating SLE patients with liver and kidney yin deficiency, which can remove toxins from the body, while anti-inflammatory and improving immune function.

3.1.4. *Warming the kidney and strengthening the spleen has a good prognosis*

In the *Jing Yue Quan Shu*, it is stated that "the treatment of water must be based on the spleen and kidneys, and the deficiency should be transformed, while the real one should be diarrhea". Li Songwei et al.^[17] randomly divided 80 patients with spleen-kidney yang deficiency type LN into two groups, and the control group was given prednisone acetate tablets (produced by Jiang Xianju Pharmaceutical Co., Ltd, 0.5 mg/kg/d, gradually reduced according to the condition) + mortifamate tablets (produced by Hunan Huana Pharmaceutical Co., Ltd, 750 mg/time, 2 times/day) + calcium, and the treatment group was combined with oral gorgonzola combination (30 g of gorgonzola, 15 g of Astragalus membranaceus, 15 g of Astragalus membranaceus, 2 times/day) on this basis. After 3 months of treatment, C3, ESR, anti-ds-DNA, IgM and urine protein quantification in the combined Gorgonzola group showed significant improvement compared with the control group, and the hormone dosage was also less than that of the control group during the whole course of treatment, which shows that the use of Gorgonzola can effectively suppress inflammation and It can be seen that the use of Gorgonzola can effectively suppress inflammation and withdraw hormones as soon as possible, which directly and effectively avoids the adverse effects produced by hormones. Zhen Wu Tang is derived from the *Treatise on Typhoid Fever* and has the effect of "warming yang and promoting water", which is a good formula for the evidence of internal stagnation of water and qi caused by deficiency of spleen and kidney yang. Su Paulin et al.^[18] randomly divided 72 patients with LN into two groups, 36 cases in the control group were given methylprednisolone tablets combined with morte-macrolide capsules (primidone), and the observation group was treated with the addition of Zhen Wu Tang (10 g each of Radix et Rhizoma rehmanniae and ginger, 15 g of Paeonia lactiflora, Poria cocos and Atractylodes macrocephala), after 8 weeks of treatment, the total effective rate of the observation group (87.90%) was higher than that of the observation group (79.40%), and the levels of toxins in the observation group, the 24h urine protein quantification values were significantly lower than those of the control group, and the values of eGFR and plasma Alb were significantly higher than those of the control group. In conclusion, Zhen Wu Tang can effectively improve the renal function of LN patients and delay the progression of LN.

3.2. *Treatment by stages*

Most physicians believe that in treating LN, patients should be treated in stages according to the specific characteristics of their disease, thus giving rise to the view of staged treatment, see Table 2. LN is divided into the early stage of lesions and the late stage of lesions^[19]. He evil qi dominates and treatment is based on clearing heat and detoxifying the toxin; in the late stage, the deficiency of positive qi is treated by benefiting qi and nourishing yin and tonifying the spleen and kidney. Zhao WJ^[20] divided the period of LN in hormonal treatment into the following three phases through TCM theory: the period of positive and negative influence, the period of negative influence, and the period of supporting positive and consolidating the root. The period of competition between good and evil is the sufficient hormone treatment period, at this time, the evil Qi enters the Blood Branch from the Wei and Qi Divisions, so the treatment should be to clear heat and cool the Blood as the main method, when the struggle between good and evil depletes Qi and Yin, so the treatment should be based on Ginseng-Qi Dihuang Tang, which has the effect of benefiting Qi and nourishing Yin; the period of the consolidation of Zheng is the period of maintenance treatment, when small doses of hormone are used, when Yin and Yang are deficient, so the treatment should be based on Double Tonic Di Gui Tang, which has the effect of both Yin and Yang. Prof. Lu Ying^[21] in the treatment of LN from rheumatism, it is recommended to reduce the disease activity during the active phase, while protecting the kidney function, and to maintain the treatment during the remission phase and exclude the early signs of internal disturbance of rheumatism. Liu Chunying^[22] divided the disease into three stages and four types of evidence during the treatment of LN with hormones, as follows: the hormone shock stage, when dampness and heat are common, and the treatment is to clear heat and dampness and cool the blood; the hormone reduction stage, when spleen and kidney qi deficiency is common, and the treatment is to tonify the spleen and kidney; the hormone maintenance stage, when qi deficiency and blood stasis are seen and liver and kidney yin deficiency with blood stasis, and the treatment is to benefit qi and activate blood and eliminate stasis or nourish the liver and kidney and benefit qi and activate blood. Zhang Duo^[23] summarized the development of LN disease as "dancing with wolves", i.e., fighting between good and evil and surviving with disease. At the onset of the disease, the urgent approach is to "fight the wolf" by clearing heat and cooling blood to detoxify; the slow approach is to "tame the wolf" by benefiting qi and nourishing yin, supplemented by clearing heat and detoxifying; the steady approach is to "tame the wolf" by warming and tonifying the yang of the spleen and kidney.

Table 2: Staged treatment by various medical practitioners

Doctor	Stages
Zhang Jinfeng	1.Active phase of the condition 2.emission
Zhao Wenjing	1.A period of contention between good and evil 2.Evil retreats into a period of righteousness 3.Fuzheng Gu current period
Liu Chunying	1.Hormonal shock phase 2.Hormonal maintenance phase
Zhang Duo	1.Acute active phase 2.Disease remission 3.Stable phase of the disease

4. Proprietary Chinese Medicine Treatment

With the development of Chinese medicine, the research of proprietary Chinese medicine has become increasingly mature. Proprietary Chinese medicine is based on the theory of Chinese medicine and combined with modern technology to realize the transformation of traditional Chinese medicine from traditional soup to other dosage forms, such as formulated granules, pills, oral liquid, capsules, etc. At the same time, it has the characteristics of convenient portability, safety and effectiveness [24]. In the treatment of LN, Zhao Wenli et al. [25] used Chinese patent medicines rationally on the basis of evidence identification, and recommended oral administration of Huangqi capsule or Kunming Shanhaitang tablets for patients with incandescent heat toxicity; Zhi Bai Di Huang Wan for patients with liver and kidney yin deficiency; Bai Ling capsule and Jin Shui Bao capsule for patients with spleen and kidney yang deficiency; and Sheng Wei injection for patients with Qi and Yin deficiency. Tu Xiao et al [26] did a retrospective analysis of 103 patients with chronic kidney disease and concluded that Kunxian capsule could effectively reduce urinary protein levels in patients with kidney disease with rapid onset of action and high safety. A large number of studies [27-29] showed that Huangkui capsule has the effect of clearing heat and detoxifying and decongesting, and has unique advantages in reducing urinary proteinuria and 24h proteinuria, as well as effectively reducing the accumulation and burden of pathological products in the kidney, further reducing BUN and Scr, escorting renal function and delaying disease progression. In a clinical study of LN patients, Qiao Jianfen et al. [30] concluded that renal heparin capsules, which have the effect of tonifying the liver and kidney and supporting the essence, can effectively reduce urinary protein, BUN, and Scr. Luo Zhen et al. [31] achieved significant clinical efficacy in the treatment of LN patients with the addition of compound nephritis tablets on top of Western medical treatment, indicating that compound nephritis tablets can delay renal fibrosis and reduce urinary protein.

5. Other treatments

5.1. Enema treatment

The operation of herbal enema is to instill herbal tonics from the anus to the lower intestine and retain them therein. The mechanism is absorption through the mucous membrane in the intestine thus relieving various inflammatory diseases. Ma Rong [32] organized 100 patients with LN and combined herbal enemas with conventional Western medical treatment, and eventually the patients in the combined herbal enema group showed a significant decrease in urine erythrocytes, 24-h urine protein, BUN, and Scr, indicating that the role of herbal enemas in the treatment of LN is considerable. Pan Jinxin et al. [33] confirmed that herbal enemas can be anti-inflammatory and protect renal function in a study on the treatment of patients with chronic renal failure.

5.2. Acupuncture and Tuina treatment

Acupuncture treatment is to further stimulate the acupuncture points through the combination of identification and selection of acupuncture points with tonic and diaphoretic techniques to achieve the purpose of unblocking the meridians, supporting the positive and eliminating the evil, and harmonizing yin and yang. Jiang Shuai et al. [34] studied the effect of acupuncture on LN through acupuncture in a mouse LN model, and it was concluded that acupuncture has the effect of warming yang and dispersing

cold, supporting the righteousness and dispelling the evil, as well as inhibiting the inflammatory response, reducing urinary protein and protecting the kidney function in the treatment of LN. Xu Tao et al. [35] concluded that the pathogenesis of SLE is closely related to the imbalance of Ying and Wei, and the main pathogenesis is Ying less and Wei fracture, and the pathological factors are mainly stasis and heat. The treatment can be done by acupuncture and moxibustion to connect the brain and kidney, communicate with Yin and Yang, and run the stilt veins of Wei Qi, thus making Ying Qi abundant, Ying and Wei harmonious, and blood flow smooth, and achieving the effect of treating SLE. Zhang Yugui et al. [36] by combining Chinese massage and tui-na with basic treatment in 40 patients with SLE and no tui-na treatment in the control group, after 1 year of treatment, the routine examination and biochemical examination of the treatment group were significantly better than before the treatment and compared with the control group, and the tui-na technique, which has the effect of moving qi and blood, and regulating tendons and dispersing knots, improved the immunity of patients to a certain extent, reduced the harm of hormone side effects on patients, and enhanced the happiness of patients' life index and quality of life.

5.3. Medicinal bath

The herbal bath therapy is based on heat fumigation to promote the flow of qi, blood, meridians and skin couples, and finally to achieve the elimination of toxins from the body, with the effect of eliminating evil, reducing swelling, lowering urea nitrogen, etc. [37]. It has the effect of eliminating evil and reducing swelling, lowering urea nitrogen and so on. Xu Minxia et al. [38] eighty-four patients with sleep disorders of yin deficiency and fire type SLE were randomly divided into two groups, in the control group, alprazolam tablets (0.4 mg/day, taken at bedtime) were used, and in the treatment group, auricular acupressure with magnetic beads + medicinal bath therapy (30 g each of chrysanthemum, calcined magnetite and calcined dragon bone, 15 g each of nightshade, yellow lily, helianthus, and raw groundnut, and 10 g each of angelica) was applied. The sleep quality was significantly better than that of the anti-insomnia drug group alone after the combination of medicinal bath therapy, and the time to sleep was less than that of the control group, in addition to relieving the patients' anxiety and depression.

6. Summary

Western medicine has many side effects in the treatment of LN, and the long-term use of hormonal drugs can lead to the occurrence of adverse reactions such as femoral head necrosis, liver damage, kidney damage and drug resistance. TCM is unique in the treatment of LN, from evidence-based treatment and phased treatment to proprietary Chinese medicine treatment and other therapies, all of which have good efficacy on LN, as well as high safety and good patient compliance, with irreplaceable effects. In conclusion, TCM has a rich source of knowledge in the treatment of LN, and the addition of TCM treatment to conventional basic treatment will alleviate patients' symptoms, improve their condition, maintain residual kidney function, and improve their survival expectation, which is worth promoting in the clinic.

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