From "Wind, Heat, Dampness, and Stasis" to Mesangial Proliferation: A Systematic Review of the Correlation between the Evolution of Traditional Chinese Medicine Pathogenesis and Micro-Pathology in IgA Nephropathy

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Abstract: IgA nephropathy (IgAN) is the most common primary glomerular disease globally, characterized by mesangial IgA deposition and clinical signs like hematuria and proteinuria. Traditional Chinese Medicine (TCM) classifies this disease under concepts such as "Kidney Wind." Contemporary TCM scholars have refined its pathogenesis into four key elements: "wind, heat, dampness, and stasis." This paper systematically reviews recent research on the correlation between TCM syndromes of IgAN and renal tissue pathology. It explores how "wind, heat, dampness, and stasis" correspond to micro-pathological changes such as mesangial proliferation and tubulointerstitial fibrosis. The study proposes a pathogenic evolution axis: "Wind-heat disturbing the kidney → Dampness and stasis binding → Kidney collateral stagnation". Research indicates that wind-heat combination often corresponds to acute mesangial cell proliferation. Dampness encumbrance is closely related to increased mesangial matrix. Stasis runs through the entire course, becoming prominent in glomerulosclerosis and fibrosis. This correlation model provides theoretical support for integrated diagnosis and treatment.

***Keywords*:** IgA nephropathy; TCM pathogenesis; wind-heat-dampness-stasis; mesangial proliferation; micro-pathology; correlation

1. Introduction

IgA nephropathy (IgAN), first described by Berger in 1968, is the most common primary glomerular disease, accounting for 30%–40% of primary glomerulonephritis [1]. Its pathological hallmark is mesangial deposition of IgA-dominant immune complexes, accompanied by mesangial proliferation and matrix expansion. Current Western treatment relies on renin-angiotensin system blockers and immunosuppressants; however, efficacy varies, and side effects remain concerns.

The TCM understanding of IgAN has evolved from "edema" to concepts like "Kidney Wind." Recently, "wind, heat, dampness, and stasis" have gained acceptance as core pathogenic elements[2]. Studies reveal that patients at different pathological stages exhibit distinct TCM patterns correlating with pathological grading[3]. This paper aims to systematically review research linking TCM pathogenesis with modern pathology, constructing a framework correlating "wind, heat, dampness, and stasis" with micro-pathological changes.

2. Evolution of the TCM Understanding of IgAN Pathogenesis

2.1 Tracing the Traditional "Kidney Wind" Theory

The "Plain Questions" states: "The symptoms of Kidney Wind are sweating, aversion to wind, facial swelling, and spinal pain." This resembles the episodic hematuria and edema seen in IgAN [4]. Zhang Zhongjing's "Synopsis of the Golden Chamber" discusses "Wind Edema," highlighting the role of wind pathogens. During the Ming and Qing dynasties, the rise of epidemic febrile disease theories provided a foundation for wind-heat pathogens invading the kidney collaterals.

2.2 Formation of the "Wind, Heat, Dampness, Stasis" Paradigm

Since the 1990s, experts have proposed that IgAN's pathogenesis centers on "wind, heat, dampness, and stasis" [5]. Specifically:

Wind: Includes external wind (triggered by infection) and internal wind, manifesting as episodic hematuria.

Heat: Often stagnant or latent heat, corresponding to inflammation from immune deposition.

Dampness: Arises from spleen and kidney dysfunction, linked to proteinuria and interstitial edema.

Stasis: Runs through the disease, manifesting as glomerulosclerosis and microthrombosis.

2.3 Staged Characteristics of Pathogenesis Evolution

Clinical observations show staging [6]:

Acute Exacerbation: Dominated by wind-heat, presenting with pharyngitis and hematuria, correlating with mesangial proliferation.

Chronic Persistent: Characterized by dampness and stasis, presenting with persistent proteinuria, correlating with matrix expansion.

Advanced Stage: Marked by stasis and deficiency, corresponding to glomerulosclerosis and fibrosis.

3. Correlation between "Wind, Heat, Dampness, Stasis" and Micro-Pathological Changes

3.1 Wind Pathogen and Mesangial Cell Proliferation, Crescent Formation

Wind's "swift and variable" nature aligns with IgAN's acute phase. Studies show patients with wind-heat syndrome often exhibit mesangial proliferation and cellular crescents [7]. A study of 236 IgAN patients found crescents in 62.3% of wind-heat patients ($P < 0.01$) [8]. Mechanistically, wind may activate the intrarenal renin-angiotensin system, promoting mesangial proliferation[9].

3.2 Heat Pathogen and Inflammatory Infiltration, Capillary Loop Necrosis

Heat pathogen corresponds to inflammatory changes. In active IgAN, capillary loop necrosis aligns with "heat toxin." Research shows TNF-α and IL-6 levels in renal tissue are elevated in patients with severe heat syndrome, correlating with the activity index ($r=0.52$, $P<0.01$) [10].

3.3 Dampness Pathogen and Mesangial Matrix Expansion, Podocyte Injury

Dampness corresponds to mesangial matrix accumulation. Patients with dampness syndrome often exhibit significant proteinuria[11]. Their degree of podocyte injury is significantly elevated [12]. Herbal formulas that eliminate dampness can reduce proteinuria, suggesting a link between dampness and matrix metabolism disorders.

3.4 Blood Stasis and Glomerulosclerosis, Tubulointerstitial Fibrosis

Blood stasis is prominent during chronic lesions. Glomerulosclerosis and fibrosis fall under "stasis obstructing collaterals." Studies confirm that patients with blood stasis syndrome show increased collagen deposition in renal tissue [13]. Herbs that invigorate blood can inhibit fibroblast activation and reduce TGF-β1 expression [14]. The blood stasis score is negatively correlated with eGFR ($r=0.61$, $P < 0.001$) [15].

4. Dynamic Correlation between Pathogenesis Evolution and Pathological Outcomes

4.1 Wind-Heat Disturbing the Kidney → Acute Active Lesions

In the initial stage, external wind-heat invades the kidney, leading to mesangial proliferation. Pathologically, this stage is characterized by active lesions, which may be reversible with timely treatment.

4.2 Damp-Heat Internally Accumulating → Mesangial Proliferation and Matrix Expansion

As the disease persists, spleen and kidney are damaged, leading to damp-heat. This stimulates mesangial cells to secrete matrix, resulting in matrix expansion. Pathologically, this involves proliferative lesions.

4.3 Blood Stasis Coagulating → Glomerulosclerosis and Fibrosis

With prolonged disease, dampness and stasis interlock, obstructing kidney collaterals. This leads to ischemic glomerulosclerosis and interstitial fibrosis, which are generally irreversible.

4.4 Deficiency as the Root, Present Throughout

Underlying these pathogenic elements, spleen and kidney deficiency consistently exists. It is the foundation for the evolution of pathogenesis and the driver of chronicity.

5. Clinical Implications and Future Perspectives

5.1 Constructing a "Syndrome-Pathology" Correlation Model

This paper proposes a correlation model

Wind → Mesangial proliferation, crescent formation

Heat → Inflammatory infiltration, capillary loop necrosis

Dampness → Mesangial matrix expansion, podocyte injury

Stasis → Glomerulosclerosis, tubulointerstitial fibrosis

5.2 Guiding Integrated Treatment Strategies

Treatment can be staged: In the acute phase, dispel wind and clear heat. In the chronic phase, eliminate dampness, resolve stasis, and supplement qi. In advanced stages, support healthy qi and resolve stasis.

5.3 Research Outlook

Current research limitations include: a lack of standardized criteria for correlating TCM syndromes with pathology; a need for large-scale prospective studies; and a need for deeper mechanistic investigation using advanced technologies like single-cell sequencing.

6. Conclusion

The four elements—"wind, heat, dampness, and stasis"—exhibit systematic correlations with modern pathological changes. The evolution of pathogenesis follows a dynamic axis aligning with the transition from active to chronic lesions. This model contributes to greater precision in integrated TCM-Western medicine treatment.

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