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Discussion on TCM Intervention Strategy for Diabetic Nephropathy Vascular Disease from the Perspective of Network Disease Theory

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Abstract: ***As a severe microvascular complication of diabetes, diabetic nephropathy is closely associated with vascular pathologies. Root-and-network theory, originating from classical Chinese medical texts, posits that meridian networks serve as microscopic pathways for qi and blood circulation, where their dysfunction can trigger various chronic diseases. This study employs root-and-network theory to systematically analyze the pathological mechanisms of diabetic nephropathy's vascular complications, proposing three key perspectives: meridian network obstruction, meridian network deficiency, and meridian network depletion. Integrating holistic TCM concepts and syndrome differentiation principles, we elaborate on therapeutic strategies including blood activation, meridian unblocking, tissue dispersion, and meridian qi supplementation. Clinical case analyses and experimental studies validate these interventions' effectiveness in improving microcirculation, reducing vascular endothelial damage, and delaying disease progression. The findings aim to establish new theoretical foundations and practical guidelines for TCM-based treatment of diabetic nephropathy's vascular manifestations.***

Keywords: Diabetic nephropathy, Vascular lesions, Network disease theory, TCM intervention strategy, Blood circulation and blood stasis.

1. Introduction

In contemporary society, with evolving lifestyles and accelerated aging, diabetes prevalence has been rising steadily. Diabetic nephropathy, as one of the most common and severe chronic complications of diabetes, continues to show concerning trends. Epidemiological studies reveal that the incidence of diabetic nephropathy among diabetes patients has been increasing significantly in recent years, now ranking among the leading causes of end-stage renal disease. This condition not only severely impacts patients' quality of life, imposing heavy financial burdens and psychological stress on families, but also drains substantial social healthcare resources.

2. Theoretical Framework Construction of Network Disease

2.1 Structure Analysis of Meridian System

The meridian system, a vital component of Traditional Chinese Medicine (TCM) theory, features intricate and sophisticated structures primarily categorized into two types: meridian networks and blood vessel networks. Meridian networks, serving as branches of the meridian system, are extensively distributed across the body's surface and internal organs. These networks perform crucial physiological functions including connecting internal and external systems, linking organ functions, and circulating qi (vital energy), blood, and body fluids. Functioning like an information network, they ensure seamless coordination between bodily parts. Blood vessel networks, conversely, focus on microscopic blood vessels that penetrate tissues and organs. These vessels deliver essential nutrients and oxygen to cells while removing metabolic waste, thereby maintaining normal physiological activities.

2.2 Core Pathogenesis of Diabetic Nephropathy

Diabetic nephropathy, a complex chronic condition, involves a dynamic progression of pathological mechanisms characterized by qi stagnation in the meridian network, blood stasis in the renal vessels, and deficiency of kidney network nourishment. In early stages, impaired qi flow causes stagnation in the renal meridians, disrupting blood circulation. As the disease advances, progressive vascular blockages form microthrombi that further impede nutrient delivery, exacerbating renal damage. In terminal stages, the core issue becomes deficient kidney network nourishment. With diminished blood supply from the renal meridians, their functional capacity progressively declines, ultimately leading to severe renal impairment.

2.3 Theory of Stage of Network Disease

According to the different stages of diabetic nephropathy, TCM proposed the theory of network disease staging. The theory divided diabetic nephropathy into three stages: early, middle and late, each of which has its own unique pathological characteristics and clinical manifestations.

In the early stages, patients primarily present with the liver-kidney qi-yin deficiency syndrome. At this phase, while the kidney network has not yet suffered significant damage, early signs of qi-yin deficiency have already emerged. Treatment should focus on nourishing the liver and kidneys, replenishing qi and yin, aiming to restore normal kidney network function and prevent further deterioration of the condition.

In the intermediate stage, patients experience progressive deterioration of symptoms characterized by the spleen-kidney deficiency syndrome. This condition arises when the spleen fails to properly transform and transport nutrients while the kidneys lose their protective function, leading to internal

retention of dampness and phlegm accumulation. The treatment strategy should focus on strengthening spleen-kidney functions, eliminating dampness, and resolving phlegm. By regulating these organ systems, we aim to optimize the body's internal environment and reduce the burden on kidney meridians.

In the advanced stages, patients exhibit severe symptoms characterized by yin-yang deficiency syndrome. At this critical phase, renal collaterals have suffered significant damage with nearly complete functional decline. Therapeutic interventions should focus on warming and tonifying yin-yang, while activating blood circulation to restore meridian function. This approach aims to restore microcirculation in renal collaterals, slow disease progression, and improve quality of life. Guided by the theory of collaterals' disease staging, we can develop more precise TCM intervention strategies, providing customized treatment plans for diabetic nephropathy patients.

3. Mechanism of Vascular Lesions in Diabetic Nephropathy

3.1 The Nature of Network Disease in Microvascular Lesions

Pathological changes in glomerular capillary loops: During the progression of diabetic nephropathy, significant pathological alterations occur in the glomerular capillary loops. These include thickening of the capillary basement membrane, increased mesangial matrix, and capillary occlusion. From the perspective of network pathology, these changes reflect blood stasis and malnutrition in the network vessels. As the pathway for qi and blood circulation, impaired network vessel function leads to obstructed blood flow, ultimately affecting normal kidney function.

Blood flow dynamics abnormalities and metabolic byproduct accumulation: Patients with diabetic nephropathy often exhibit hemodynamic abnormalities such as intraglomerular hypertension, hyperperfusion, and hyperfiltration. These pathophysiological changes increase pressure within glomerular capillary walls, leading to endothelial cell damage and basement membrane injury. Concurrently, the accumulation of metabolic byproducts like advanced glycation end products (AGEs) further damages glomerular capillaries. This combined damage exacerbates collateral vascular obstruction and nutrient deprivation in the glomeruli, creating a self-perpetuating vicious cycle.

3.2 The Inflammation-oxidative Stress-fibrosis Axis

Immune-inflammatory cell infiltration: In the pathogenesis of diabetic nephropathy, immune inflammatory cells play a pivotal role. These cells, including monocytes, macrophages, and T lymphocytes, secrete various inflammatory factors such as tumor necrosis factor-α and interleukin-6. These cytokines further activate inflammatory responses, leading to renal tissue damage and fibrosis. From the perspective of network pathology, the inflammatory response can be viewed as a manifestation of external pathogenic factors invading the network vessels, while the release of inflammatory cytokines exacerbates blood stasis and vascular damage within these vessels.

Elevated oxidative stress markers: Oxidative stress serves as another critical mechanism in the pathogenesis of diabetic nephropathy. In diabetic conditions, hyperglycemia leads to increased levels of oxidative stress markers such as superoxide anions and hydrogen peroxide. These oxidative stress products damage renal tissue structures and impair cellular functions, thereby promoting fibrosis development. According to the theory of network disease (luobing), oxidative stress manifests as excessive heat accumulation in the network vessels, which subsequently causes blood stasis and malnutrition within these vessels.

Extracellular matrix deposition: Under the combined effects of inflammation and oxidative stress, extracellular matrix (ECM) accumulates in renal tissues. These deposits, including collagen and fibronectin, contribute to tissue hardening and fibrosis. From the perspective of network pathogenesis theory, ECM deposition represents a severe manifestation of meridian obstruction, which further impedes the circulation of qi and blood as well as nutrient supply.

3.3 Neurovascular Unit Dysfunction

Enhanced Sympathetic Nervous System Activity: In the pathogenesis of diabetic nephropathy, increased sympathetic nervous activity serves as a key mechanism. This heightened activity leads to renal vasoconstriction and reduced blood flow, thereby exacerbating ischemia and hypoxia in renal tissues. Such compromised oxygenation and blood supply further aggravate blood stasis and malnutrition in the collaterals. From the perspective of collaterals pathology, this sympathetic hyperactivity manifests as a manifestation of yin-yang imbalance caused by external pathogenic factors invading the collaterals.

Endothelin System Imbalance: Endothelin, a potent vasoconstrictive peptide, plays a crucial role in the pathogenesis of diabetic nephropathy. In diabetic conditions, endothelin system imbalance leads to renal vascular constriction and reduced blood flow. This contraction and reduction further exacerbate ischemic and hypoxic states in renal tissues, thereby aggravating blood stasis and tissue damage. According to the theory of network disorders, endothelin system imbalance can be interpreted as a manifestation of yin-yang imbalance caused by impaired circulation of qi and blood within the meridian network.

4. TCM Intervention Strategy System

4.1 Differentiation and Treatment by Stages

Diabetic nephropathy (DN), categorized under TCM concepts such as "xiao ke" (excessive thirst), "yu zuo" (urinary turbidity), "xi xu" (edema), and "xu lao" (deficiency-laden fatigue), involves vascular pathogenesis rooted in "chronic xiao ke leading to qi-yin depletion, which gradually affects meridian networks and causes kidney network obstruction." The disease progression follows a pattern of "qi-yin deficiency → spleen-kidney deficiency → qi-blood exhaustion and internal toxin accumulation," which closely aligns with the evolution of meridian disorders described as

"meridian qi stagnation → meridian blockage → meridian congestion → meridian obstruction."

4.2 Early Intervention Programmes

In the early stage corresponding to Mogensen stage I-III (from hyperfiltration of glomeruli to microalbuminuria), the disease site is mainly in the liver and kidney, and the pathogenesis is based on "liver and kidney yin deficiency, qi and yin deficiency, and collaterals qi stagnation".

Liver and Kidney Tonic Formula: Suitable for liver-kidney yin deficiency syndrome, symptoms include soreness and weakness in the lower back and knees, dizziness with tinnitus, dry mouth and throat, red tongue with scanty coating, and fine rapid pulse. The formula consists of 15g of prince ginseng, 12g of ophiopogon japonicus, 15g of raw rehmannia root, 10g of cornus fruit, 12g of barbary wolfberry, 15g of poria, 10g of moutan bark, and 15g of danshen. Formula Explanation: Prince ginseng tonifies qi and generates body fluids; Ophiopogon japonicus and raw rehmannia root nourish yin and moisten dryness, collectively replenishing the yin of liver and kidney; Cornus fruit and barbary wolfberry tonify liver and kidney while consolidating essence; Poria strengthens spleen and drains dampness, preventing excessive yin nourishment from impairing spleen function; Moutan bark and danshen cool blood and activate circulation, initially resolving blood stasis in collaterals, thus achieving the dual effects of nourishing liver and kidney and promoting collaterals.

4.3 Interim Programme of Intervention

In the middle stage, corresponding to Mogensen stage iv (clinical proteinuria), the disease position involves the spleen and kidney, and the pathogenesis progresses to "spleen and kidney deficiency and aggravated blood stasis", which can be seen as increased proteinuria, edema, fatigue, etc.

Wenren Jianpi Formula: This formula is indicated for spleen-kidney yang deficiency syndrome, with symptoms including cold aversion and limbs chills, cold pain in the lower back and knees, abdominal distension with loose stools, lower limb edema, pale swollen tongue with white slippery coating, and deep slow pulse. Ingredients: Epimedium 15g, Psoralea 12g, Atractylodes 15g, Poria 20g, Chinese Yam 15g, Alisma 10g, Cinnamon Twig 8g, Tangerine Peel 10g. Epimedium and Psoralea warm and tonify kidney yang; Atractylodes, Poria, and Chinese Yam strengthen spleen qi; Alisma promotes diuresis and reduces edema; Cinnamon Twig warms yang and transforms qi; Tangerine Peel regulates qi and harmonizes the middle. Together they achieve the effects of warming kidneys, strengthening spleen, transforming qi, and promoting water metabolism, while addressing the functions of "kidney governing water" and "spleen transforming water-dampness," thereby improving kidney network obstruction caused by water-damp stagnation.

4.4 Late-stage Intervention Program

The late stage corresponds to Mogensen stage v (end-stage renal disease), and the pathogenesis is "blood and qi deficiency, blood network stasis, turbid toxin retention", accompanied by renal failure, anemia, turbid toxin retention, etc.

Qi-Boosting and Blood-Nourishing Formula for Tendon Knots: Suitable for qi-blood deficiency and collaterals stagnation syndrome, with symptoms including pale complexion, palpitations, shortness of breath, soreness in waist and knees, limb numbness, pale purple tongue with ecchymosis, and fine-thready pulse. The formula contains 30g raw Astragalus membranaceus, 15g Chinese angelica root, 15g Cuscuta seed, 15g prepared rehmannia root, 12g white peony root, 20g chicken blood vine, 10g sparganium root, 10g zedoary rhizome, and 6g leech (processed into powder for oral administration). Raw Astragalus and Chinese angelica root tonify qi and nourish blood; Cuscuta seed and prepared rehmannia root replenish kidney essence; white peony root and chicken blood vine nourish and activate blood circulation; sparganium root, zedoary rhizome, and leech resolve blood stasis and disperse nodules. This formula addresses advanced-stage collaterals stagnation and accumulations through a combination of purgative and tonic effects, achieving the dual therapeutic goals of qi-tonifying blood-nourishing and blood-activating nodule-dispelling.

4.5 Multidimensional Intervention Techniques

4.5.1 Needle therapy

Based on the theory of "meridian and vein", acupuncture and moxibustion can regulate qi and blood and unblock kidney network.

Acupoint selection principles: Focus on points along the Foot-Taiyin Spleen Meridian, Foot-Shaoyin Kidney Meridian, and Ren-Du Meridians. Zusanli (Confluent Point of Foot-Yangming Stomach Meridian) strengthens spleen qi, generates blood and qi, and nourishes kidney meridians. Shenshu (Back-Shu Point of Bladder Meridian) warms and replenishes kidney qi, replenishes essence and marrow, and improves kidney meridian deficiency. Taixi (Original Point of Kidney Meridian) nourishes kidney yin, unblocks meridians for pain relief, and regulates kidney meridian yin-yang balance. Supplementary points may include Sanyinjiao (strengthens spleen/kidney and activates blood circulation), Xuehai (activates blood circulation to resolve stasis), and Guanyuan (warms and replenishes primordial qi).

Acupuncture Techniques: For deficiency syndromes, apply tonifying methods (twisting and rotating techniques, lifting-and-inserting techniques). For excess syndromes, use draining methods (twisting and draining techniques, lifting-and-inserting techniques). For mixed syndromes, employ balanced tonification and drainage. Combined with electro-acupuncture (continuous wave at 2-5Hz frequency, intensity adjusted to patient tolerance, needle retention for 30 minutes) enhances acupoint stimulation, promotes blood and qi circulation, and improves renal network microcirculation.

Moxibustion for Warmth and Meridian Regulation: The Guanyuan point (Ren Meridian acupoint), known as the "root of primordial qi", can be treated with either ginger-separated moxibustion (using 0.3cm thick ginger slices and jujube-nut-sized moxa cones, 5-7 cones per session) or gentle

moxibustion (placing moxa sticks 3-5cm from skin surface for 20-30 minutes). This therapy enhances yang energy transformation, promotes diuresis, and reduces edema. It is recommended for 2-3 sessions weekly to address conditions caused by spleen-kidney yang deficiency and water-dampness obstructing kidney meridians.

4.5.2 External therapy

Through skin and acupoint administration, it can reach the disease directly, avoiding oral drugs to aggravate the burden of gastrointestinal and renal network.

Traditional Chinese Medicine (TCM) Iontophoresis: Take 10ml of Danshen Injection and dilute with 20ml of normal saline. Soak the electrode pads and apply them to both sides of the Shenshu acupoints. Connect to an iontophoresis device (current intensity 0.05-0.1mA/cm², 20-30 minutes per session, once daily). Danshen promotes blood circulation and resolves stasis while activating meridians and activating collaterals. The iontophoresis method delivers medicinal ions through direct current via skin meridians to the kidney meridian, improving renal microcirculation and reducing urinary protein levels.

Acupoint Patch Therapy: Take equal portions of rhubarb and mirabilite, grind into powder, sieve, and mix with warm water to form a paste. Apply the mixture to the Shenque point (navel) and bilateral Shenshu points, covering with gauze and securing with adhesive tape. Leave on for 4-6 hours daily. Rhubarb clears heat, promotes bowel movements, and resolves blood stasis, while mirabilite softens hard masses and reduces swelling. When applied externally through acupoint penetration, they work synergistically to eliminate turbidity and unblock meridians. This therapy is suitable for moderate to advanced cases with combined turbidity-stasis accumulation.

Chinese Herbal Enema: Take 15g raw rhubarb, 30g oyster shell, 20g dandelion, and 20g Junexue (a traditional Chinese herb). Decoct to prepare a 100-150ml solution. When cooled to 38-40℃, have the patient lie left lateral with buttocks elevated 10cm. Insert an anal tube 15-20cm long and slowly administer the enema. Retain for 30-60 minutes once daily. This treatment is suitable for patients with advanced internal turbid toxin accumulation who experience nausea/vomiting and inability to eat. It promotes intestinal detoxification, reduces serum creatinine and blood urea nitrogen levels, and alleviates renal network damage caused by turbid toxin accumulation.

4.5.3 Dietary therapy

Combined with the theory of “food and medicine are the same”, dietary regulation can be used to improve kidney network qi and blood and reduce damage.

(1) Medicinal food recipes

Astragalus Carp Soup Ingredients: Astragalus root (30g), carp (1 whole, approx. 500g), ginger slices (3), red dates (5). Instructions: Clean and cut the carp into pieces after removing scales and innards. Simmer with astragalus, ginger, and dates over low heat for 1 hour, then season with salt. Benefits: Astragalus boosts energy and promotes diuresis to reduce swelling, while carp strengthens spleen function, regulates fluid metabolism, and aids lactation. This duo works synergistically to enhance vitality, strengthen digestion, and improve circulation. Ideal for moderate-stage patients with edema and fatigue, recommended 2-3 times weekly.

Barbary Wolfberry and Yam Porridge: Ingredients: 15g of Barbary wolfberry, 30g of yam, 50g of japonica rice. Preparation: Peel the yam and cut into chunks. Cook it with the Barbary wolfberry and japonica rice to make porridge. Consume once daily for breakfast. Benefits: Barbary wolfberry nourishes the liver and kidneys and enhances vision clarity; yam strengthens the spleen and kidneys while consolidating essence; japonica rice invigorates qi and harmonizes the middle energizer. Suitable for early-stage liver-kidney yin deficiency and dual deficiency of spleen-kidney qi and yin, and can be taken long-term.

4.5.4 Exercise prescription

“Movement generates yang” and “blood and qi are smooth when they are unblocked”. Reasonable exercise can unblock meridians, regulate blood and qi, and improve kidney network obstruction.

Traditional exercise methods: Guiding techniques such as Baduanjin (Eight Pieces of Brocade) and Tai Chi, characterized by gentle movements that emphasize “body regulation, breath control, and mind cultivation.” Baduanjin includes exercises like “Two Hands Supporting Heaven to Regulate Triple Burner” (regulating triple burner qi), “Single Lift for Spleen-Stomach Regulation” (strengthening spleen qi), and “Two Hands Grasping Feet to Strengthen Kidneys and Waist” (nourishing kidney qi and unblocking lumbar meridians). Recommended practice 1-2 times daily for 15-20 minutes each session. Tai Chi practitioners should select the Simplified 24-Form routine, focusing on dynamic transitions between solid and empty postures while sinking qi to the dantian. Through physical movements, it promotes blood circulation, enhances kidney microcirculation, and benefits patients at all stages except those with severe edema or heart failure in advanced stages.

Aerobic exercises: Low-intensity activities such as swimming, walking, and cycling should total at least 150 minutes weekly, with each session lasting 30-40 minutes. Maintain heart rate within the target range of (220-age) × (50%-70%). Swimming’s buoyancy reduces joint strain while enhancing overall blood circulation. Easy-to-follow walking can be paired with breathing techniques (e.g., inhaling for 4 steps, exhaling for 6 steps) to boost lung and kidney function. Avoid overexertion during workouts. If symptoms like chest tightness or worsening swelling occur, stop immediately.

5. Clinical Practice Standards

5.1 Diagnostic and Therapeutic Procedures

Screening and Evaluation: Diabetic patients (particularly those with type 2 diabetes mellitus with a disease duration exceeding 5 years) should undergo regular screening of the

urine microalbumin/creatinine ratio (UACR) at least once annually. Both morning and random urine samples are acceptable. The normal UACR range is <30mg/g, with 30-300mg/g considered mild albuminuria (a critical threshold for early intervention), while>300mg/g indicates significant albuminuria. Concurrent testing should include blood glucose levels (fasting and 2-hour postprandial), glycated hemoglobin (HbA1c), liver and kidney function tests, lipid profile, and blood pressure to comprehensively assess overall health status.

Staging Criteria: The Mogensen staging system corresponds to the latent phase of Luo disease (Kidney Meridian Syndrome). Stages are defined as follows: Stage I (Glomerular Hyperfiltration Phase) -latent stage; Stage II (Normal Proteinuria Phase) -early Luo disease (pre-accumulation phase); Stage III (Microalbuminuria Phase) -progressive Luo disease (initial obstruction phase); Stage IV (Clinical Proteinuria Phase) -mid-stage Luo disease (worsened obstruction); Stage V (End-stage Renal Disease) -advanced Luo disease (accumulated obstruction with internal toxin accumulation). Clinical evaluation requires comprehensive assessment of symptoms and tongue-pulse patterns: Early stage presents with red tongue with scant coating and rapid thready pulse; Mid-stage shows pale swollen tongue with petechiae and deep weak pulse; Late stage manifests as purplish dark tongue with thick greasy coating and stiff pulse.

Intervention Timing: Emphasizing “early screening, early diagnosis, and early intervention”, the optimal intervention window is during the microalbuminuria stage (Mogensen III stage/progressive nephropathy phase), when renal network damage remains mild. This stage allows reversal or progression delay through qi-tonifying yin-nourishing therapies and blood circulation activation. The massive albuminuria stage (IV) requires multidimensional interventions combining medications, acupuncture, and topical treatments. For end-stage renal disease (V stage), the focus shifts to delaying progression and improving quality of life through replacement therapies like dialysis or transplantation.

5.2 Notes

Medication Contraindications: Strictly avoid using herbs containing aristolochic acid (e.g., Gansu Coptis, Pseudostellaria heterophylla, Hedyotis diffusa, and Uncaria rhynchophylla), as these may cause renal interstitial fibrosis and irreversible kidney damage. Use with caution medications that are bitter-cold in nature and may irritate the stomach or act as heavy metal stabilizers (e.g., Aconitum carmichaeli and Aconitum racemose, which require proper processing and should be started at low doses with continuous monitoring of heart rate and blood pressure). Patients in advanced stages should avoid nephrotoxic Western medications (e.g., aminoglycoside antibiotics and nonsteroidal anti-inflammatory drugs). When combining Chinese and Western medications, allow 1-2 hours between administration to prevent drug interactions.

Contraindications for Acupuncture: 1) Hemostatic disorders (platelet count <50×10^9/L, INR>1.5); 2) Skin infections or ulcers; 3) Severe diabetic foot; 4) Contraindicated during pregnancy. 5) Use with caution in cases of needle fainting, hunger, or fatigue. 6) During acupuncture, avoid major blood vessels and internal organs. For kidney-related acupoints (e.g., Shenshu), perform oblique or horizontal insertion with depth <1.5 cun (1.5 inches) to prevent renal injury.

Dietary Restrictions: Strictly limit high-potassium foods (bananas, oranges, spinach, potatoes, seaweed, etc.) in advanced renal insufficiency (eGFR<30ml/min/1.73m²), with daily potassium intake <2000mg. Restrict high-phosphorus foods (egg yolks, animal organs, nuts) to prevent phosphorus retention that may worsen renal osteodystrophy. Avoid spicy irritants (chili peppers, Sichuan peppercorns), overly salty foods (pickled vegetables, preserved sauces), and excessively sweet items (pastries, honey). Quit smoking and limit alcohol consumption to reduce nephrotoxicity.

6. Conclusions

Through in-depth analysis of TCM theories regarding network diseases, we have identified that collaterals (luomai) – the microchannels governing qi and blood circulation – play a pivotal role in diabetic nephropathy development. The vascular complications in this condition essentially manifest as pathological blockages in collaterals and impaired blood flow. TCM employs therapeutic principles like activating blood circulation, resolving stasis, and dispersing nodules to significantly improve microcirculation in collaterals, thereby enhancing qi-blood flow and alleviating vascular symptoms. Specifically, TCM practitioners may utilize blood-activating formulas such as Xuefu Zhuyu Decoction (Blood Mansion Stasis-Resolving Decoction) to regulate qi-blood balance. When combined with external therapies like acupuncture and tuina (acupressure), these approaches further stimulate meridian energy, promote collateral repair, and provide comprehensive TCM interventions for diabetic nephropathy patients.

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