Research on the "Stomach - Knee Axis" and the Practice of "Stomach and Knee Joint Treatment" Based on the "Combined Bi of Body Constituents and Zang Organs" Theory

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Abstract The existence of the "stomach-knee axis" and the potential independent association between "*Helicobacter pylori* (Hp) infection and knee osteoarthritis (KOA)" have been substantiated through multiple lines of evidence, including epidemiological studies of the "stomach-knee axis", investigations into the pathological mechanisms linking "Hp infection and arthritis", as well as research on co-treatment drugs and the anti-inflammatory mechanisms relevant to "gastritis and arthritis". The investigation into "stomach and knee joint treatment" is grounded in the concept that the "stomach-knee axis" aligns with the "combined bi of body constituents and zang organs" theory. Clinical cases have demonstrated that therapeutic strategies of "stomach and knee joint treatment" can mitigate KOA damage by modulating the "stomach-knee axis" and eradicating Hp infection in the stomach. This study aims to contribute novel insights into the cross-system treatment of KOA. Further investigation into the "stomach-knee axis" may yield innovative strategies for the prevention and management of KOA, potentially through the eradication of Hp.

Key words Stomach, Knee, *Helicobacter pylori* (Hp), Knee osteoarthritis (KOA), Combined bi of body constituents and zang organs, Stomach and knee joint treatment

1 Introduction

In recent years, following the introduction of the "gut-joint axis" concept, research exploring the relationship between the digestive tract microenvironment and osteoarthritis (OA) has emerged as a prominent interdisciplinary field[1-2]. There exists a notable theoretical convergence between the theory of "combined bi of body constituents and zang organs" in traditional Chinese medicine (TCM) and the "stomach-intestine-joint axis". This convergence offers a novel perspective for investigating the mechanistic association between the "stomach-knee axis", *Helicobacter pylori* (Hp) infection in the stomach, and knee osteoarthritis (KOA). Chronic gastritis has been confirmed to frequently coexist with OA[3]. However, the specific mechanisms underlying KOA induced by the "stomach-knee axis" and Hp infection in the stomach require further elucidation. This article aims to explore these aspects in detail.

2 "Stomach-knee axis"

Rheumatism frequently manifests with gastrointestinal symptoms[4], and conversely, gastrointestinal disorders can contribute to the development of arthritis[5]. Dysbiosis of the intestinal microbiota and the metabolic byproducts of altered flora activate the body's immune response, thereby exacerbating inflammation and joint damage of OA and rheumatoid arthritis (RA) via the "gut-joint axis"[6-7]. In clinical practice, it has been observed that patients with chronic gastritis, particularly those infected with Hp, exhibit significantly earlier onset or more severe knee joint damage compared to their counterparts without Hp infection. Several pharmacological treatments targeting both "gastritis and arthritis" have demonstrated efficacy in eradicating Hp while concurrently alleviating arthritic symptoms. Hp has been identified in numerous studies as being associated with various extragastric diseases and rheumatic conditions[8-9]. Hp is recognized among the microorganisms that may act as triggers for arthritis[10]. Consequently, the concept of the "stomach-knee axis" has been proposed.

The "stomach-knee axis" represents an advanced research framework building upon the "gut-joint axis", integrating interdisciplinary approaches across digestion, joint, rheumatology, immunology, and multi-omics. The central concept involves investigating the interaction between "Hp infection and KOA" through a systems biology lens. Fundamentally, this approach aims to develop a mechanistic model that transcends "individual organs and limbs", thereby facilitating the creation of targeted OA diagnostic and therapeutic strategies focused on the preventive intervention and management of Hp.

2.1 Epidemiology of "stomach-knee axis" Chronic gastritis has been confirmed to frequently coexist with OA[3]. A retrospective cohort study conducted in Germany reported that 36.2% of patients newly diagnosed with OA experienced medium- to long-term sick leave, with comorbid gastritis and duodenitis showing a strong association with this outcome[11]. A large-scale epidemio-

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logical case-control study conducted in the United Kingdom reported an odds ratio (OR) of 1.98 for concurrent gastritis in patients with OA, indicating that gastritis constitutes a risk factor for OA[12]. Specifically, Hp infection was observed in 39.9% of OA patients[13], with 40% of these patients exhibiting both Hp infection and endoscopic alterations[14].

2.2 Pathological mechanism of "Hp infection and arthritis" Hp is initially recognized by the gastric mucosal epithelium, which triggers the activation of the innate immune response, followed by the engagement of the adaptive immune system. Individuals with persistent Hp infection demonstrate elevated levels of chronic immune inflammation[15], and the prevalence of autoimmune diseases increases subsequent to Hp infection[16]. Hp induces the citrullination of cellular proteins by upregulating protein arginine deiminase type 4 (PAD4), thereby exacerbating RA[17-18]. The levels of anti-citrullinated keratin 1 antibody (Cit-K1) in the serum and synovial fluid of RA patients infected with Hp are significantly elevated[17]. Furthermore, Hp contributes to the dysregulated immune cascade involved in the onset of psoriasis[19].

Helicobacter pylori neutrophil-activating protein (HP-NAP) is a virulence factor of Hp. In addition to activating innate immunity, HP-NAP induces type I T helper cell responses, thereby mediating adaptive immunity. Its pro-inflammatory properties contribute to its involvement in various diseases[20]. Urease is another essential component of Hp virulence. Notably, the urease of *Yersinia enterocolitica* is recognized as a key factor in the pathogenesis of infection-induced reactive arthritis[21].

The mechanism by which Hp contributes to OA involves the induction of systemic low-grade inflammation and molecular mimicry[13], resulting in the release of multiple inflammatory cytokines[22], including interleukin-18 (IL-18), interferon-gamma (IFN-γ), interleukin-1β (IL-1β), interleukin-6 (IL-6), and interleukin-8 (IL-8). These cytokines promote OA-related inflammation through the circulatory system[23], ultimately leading to cartilage degeneration. Additionally, Hp infection may exacerbate OA pathology by influencing calcium-phosphorus metabolism and insulin sensitivity[24].

2.3 Co-treatment of "gastritis and arthritis" and anti-inflammatory mechanism of drugs Intervention strategies targeting microorganisms have demonstrated feasibility in the treatment of certain forms of inflammatory arthritis[25]. Rebamipide, a gastric mucosal protective agent commonly used for gastritis and gastric ulcers, has been shown to possess anti-inflammatory properties[26]. Specifically, rebamipide mediates cartilage protection and downregulates receptor activator of nuclear factorκ-light-chain-enhancer of activated B cells (RANK)-mediated osteoclast generation, thereby alleviating mandibular condylar degeneration in mouse models of temporomandibular joint osteoarthritis (TMJ-OA)[26]. Furthermore, rebamipide inhibits oxidative damage, restores extracellular matrix homeostasis in articular chondrocytes, and mitigates subchondral bone loss by suppressing osteoclast activation. Therefore, rebamipide is a promising therapeutic approach for TMJ-OA[26].

Ginger exhibits properties that eliminate free radicals, provide antioxidative effects, and inhibit lipid peroxidation. It is utilized in the treatment of arthritis and rheumatism and has been shown to effectively prevent Hp-induced gastric ulcers in experimental animal models[27]. Additionally, dandelion demonstrates significant preventive and therapeutic effects on gastritis, colitis, and arthritis in animal and cellular disease models[28]. These effects are likely attributable to its anti-inflammatory, antioxidant, and anticancer activities. *Ranunculus ternatus* is frequently employed in the treatment of conditions such as gastritis and OA. It has been shown to reduce inflammatory mediators and effector substances and is considered a potential inhibitor of TNF-α and an antioxidant[29]. Ginsenoside Rc has demonstrated anti-inflammatory effects in gastritis and arthritis, exhibiting inhibitory activity against TNF, IL, and IFN. Additionally, it can decrease the phosphorylation of Tank-binding kinase 1, IFN regulatory factor-3, and activating transcription factor-2 in the joints of mice with hepatitis[30]. Celery seed extract (CSE) has demonstrated efficacy in inhibiting arthritis and alleviating pain in polyarthritis models[31]. Additionally, CSE has been shown to prevent and/or mitigate gastric irritation induced by non-steroidal anti-inflammatory drugs and exhibits a specific inhibitory effect against Hp[31]. Consequently, CSE may be utilized in the treatment of arthritis and other inflammatory conditions[31]. The aforementioned Chinese medicines or extracts have the potential to modulate gastric microbiota, inhibit Hp infection, and thereby influence the progression of KOA[32].

2.4 "Stomach-knee axis" study based on "Hp infection and KOA" Based on studies investigating the epidemiology of the "stomach-knee axis", the pathological mechanisms of "Hp infection and arthritis", the co-treatment of "gastritis and arthritis", and the anti-inflammatory mechanisms of relevant drugs, an interaction between Hp infection and KOA spanning "individual organs and limbs" has been established. Hp is a microorganism that may trigger KOA, with its pathological mechanism involving multiple interacting factors, including molecular mimicry, chronic inflammation, and direct induction by virulence factors. This constitutes the underlying mechanism of the "stomach-knee axis" model. Numerous pharmacological agents used in the co-treatment of "gastritis and arthritis" possess anti-inflammatory and antioxidant properties, which can eradicate Hp while alleviating arthritic symptoms. The concept of the "stomach-knee axis" aligns with the theory of "combined bi of body constituents and zang organs" in TCM, as well as with clinical practices of "stomach and knee joint treatment".

3 Stomach and knee from the perspective of "combined bi of body constituents and zang organs" in TCM

The fundamental principle underlying the "stomach and knee joint

treatment" is based on the concept that the stomach is situated in the middle energizer of the human body, corresponding anatomically to the knee joint located in the central segment of the limb. This relationship embodies the theoretical framework of central harmony in TCM, which emphasizes the earth element's virtue at the center, the mutual seeking of homogeneous qi, and the balanced qi flow within the triple burners[33]. The stomach is classified as a "zang organ", and the knee joint is part of "body constituents". The foot Yangming stomach meridian and the knee joint together constitute an integrated internal-external system network, aligning with the theory of "combined bi of body constituents and zang organs"[34].

The stomach is situated in the middle energizer and, in conjunction with the spleen, is considered "the foundation of the acquired constitution". It functions to receive and transform food into the essence of water and grains, thereby producing qi and blood that nourish the muscles and bones. The transformation and transportation functions of the spleen and stomach have a direct impact on the muscles, bones, and joints. The *Su Wen · Taiyin Yangming Lun* (*Plain Questions · On Taiyin and Yangming Meridians*) states that all limbs derive their qi from the stomach, and cannot receive the qi of water and grains. Consequently, bones and muscles lack the qi necessary for nourishment, resulting in impaired functionality. Specifically, the knee, which houses the muscles, depends on the nourishment of qi and blood supplied by the stomach meridian. Therefore, the *Su Wen · Jingmai Bielun* (*Plain Questions · Discussion on the Divergence of Meridians*) records that food qi enters the stomach, essence disperses through the liver, and surplus qi permeates the muscles.

The stomach and the knee joint are physiologically interconnected through the meridian and muscles along the regular meridians. According to the *Su Wen · Wei Lun* (*Plain Questions · Treatise on Wasting Diseases*), the Yangming meridian is considered the sea of the Five Zang and Six Fu organs; it governs the moistening of the Zongjin, which in turn restrains the bones and facilitates joint movement. Dysfunction of the foot Yangming stomach meridian and its associated pathological changes frequently result in patellar and knee pain. The *Ling Shu · Jing Mai* indicates that disturbances in the foot Yangming stomach meridian can manifest as swelling and pain in the knee and patella. The *Huangdi Neijing Taisu*, authored by the Sui Dynasty scholar Yang Shangshan, indicates that a soft and scattered pulse in the stomach region may lead to food obstruction or stagnation, as well as pain in the patellar area. When the stomach is unable to properly process water and grains due to deficiency, food accumulates within the stomach, leading to obstruction and associated pain. Because the related meridian passes through the knee, this condition may also present as patellar pain. The *Zabing Yuanliu Xizhu · Xibing Yuanliu*, written by the Qing Dynasty scholar Shen Jin'ao, records that crane-knee wind initially presents as damp-heat in the Yangming meridians.

Clinically, methods involving "stomach and knee joint treatment" are frequently employed to address knee arthralgia[32,35]. The *Mingyi Lei'an · Xitong*, authored by the Ming Dynasty scholar Jiang Huan, documents a case of a woman who experienced chronic knee pain and difficulty walking. The examination revealed six pulses that were deep and weak. Wang Shishan diagnosed the condition as spleen-stomach vacuity cold, resulting in qi and blood failing to nourish the muscles. He prescribed Fuzi Lizhong Tang, and after one month of treatment, the pain was alleviated. The *Suwen · Gukong Lun* states that knee pain, accompanied by pain extending to the shin resembling a fracture, should be treated by targeting Zhongliao on the Yangming meridians.

4 Case practice and analysis of "stomach and knee joint treatment"

Patient Hao was a 47-year-old female who presented for the first time on October 10, 2023. Chief complaints included recurrent epigastric distension and pain persisting for 10 years, as well as bilateral knee joint pain for 3 years, which had worsened over the past month. History of present illness: the patient had a 10-year history of epigastric distension and pain, attributed to a prolonged irregular diet and a preference for raw and cold foods. These symptoms were accompanied by acid reflux and heartburn. The patient sought medical care at a local hospital, where a diagnosis of "chronic gastritis" was established. Treatment with oral Omeprazole enteric-coated capsules and Xiangsha Yangwei Pills resulted in symptom relief. During this period, the aforementioned symptoms recurred repeatedly, with exacerbations triggered by consumption of raw and cold foods. The patient intermittently used the previously mentioned medications for symptomatic relief. Approximately 3 years ago, the patient began to experience progressive pain in both knee joints, which intensified during stair ascent and descent; however, she did not seek medical evaluation at that time. One month prior to presentation, the patient sought medical attention due to excessive intake of raw and cold fruits, which aggravated the epigastric distension and pain, as well as the swelling and pain in the knee joints, thereby impairing her daily activities and ambulation. Past medical history, allergy history, and family history: presenting symptoms included distension and pain in the epigastric and abdominal regions, accompanied by belching and acid reflux. She experienced swelling and pain in both knee joints, resulting in difficulty walking, as well as challenges in squatting or standing up after periods of rest or in the morning, which adversely impacted daily activities and sleep quality. Additional symptoms comprised poor appetite, disturbed sleep, fatigue, loose stools, and mildly yellow urine. Physical examination: tenderness in the epigastric region (±), swelling and tenderness in both knee joints (+), floating patellar test in both knee joints (±), and crepitus in both knee joints (+). Additionally, the tongue was swollen with a pale body, exhibiting a patchy yellow greasy exfoliative coating, and the pulse was wiry

and slippery. Visual Analogue Scale (VAS) for knee joint pain was recorded at 9 points, while the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was 95 points. Auxiliary examinations: digital radiography (DR) of both knee joints revealed joint space narrowing, osteophyte formation along the articular surfaces, sharpening of the tibial intercondylar ridge accompanied by osteophyte development, and osteosclerosis at the inferior aspects of the articular bone ends. Gastroscopy indicated chronic superficial gastritis in the active stage, with a Hp DOB value of 41.8. Western medical diagnoses: chronic superficial gastritis and knee osteoarthritis. TCM diagnoses: epigastric pain, knee pain, damp-heat accumulation in the spleen and stomach, and knee pain attributed to pathogenic factors. The Western medicine treatment plan involved administration of anti-Hp triple therapy, consisting of clarithromycin, amoxicillin, and omeprazole, with a treatment duration of 21 d. The therapeutic principles of TCM included warming yang, eliminating dampness, clearing heat, and alleviating arthralgia. The prescribed treatment consisted of a modified Wuling Powder combined with Juanbi Decoction. The prescription comprised the following ingredients: 18 g of Cinnamomi Ramulus, 15 g of Poria, 15 g of Rhizoma Atractylodis Macrocephalae, 20 g of Radix Codonopsis, 10 g of Rhizoma Zingiberis, 15 g of Radix Angelicae Pubescentis, 6 g of Asari Radix et Rhizoma, 6 g of Cortex Cinnamomi, 15 g of Radix Gentianae Macrophyllae, 15 g of Caulis Sinomenii, 15 g of Radix Achyranthis Bidentatae, 10 g of Flos Lonicerae, 15 g of Radix Angelicae Sinensis, 6 g of Fructus Amomi, 10 g of Fructus Hordei Germinatus, and 10 g of Radix Glycyrrhizae. A total of 10 doses were prepared, each to be decocted with water for oral administration. One dose was administered daily, with the decoction prepared in the morning and evening and divided into two servings. After administering 10 doses, the patient no longer experienced distension or pain in the epigastric and abdominal regions. Occasional episodes of belching and acid reflux were reported. Swelling and pain in the knee joint were markedly reduced. The patient's mobility improved, allowing for easier walking as well as the ability to squat and stand without difficulty. Additionally, the patient exhibited improvements in appetite, sleep quality, and overall mental state. Bowel movements were normal, and urination was unremarkable. The tongue appeared swollen with a pale body and exhibited a diminished greasy exfoliative coating, while the pulse was wiry and slippery. Following the adjustment of the aforementioned prescription and the administration of 10 additional doses, the patient reported no discomfort in the epigastric region, absence of swelling or pain in the knee joint, improved ambulation, and demonstrated good appetite, sleep quality, and mental state. Furthermore, both urination and defecation were normal. Physical examination: tenderness in the epigastric region (-), swelling and tenderness in both knee joints (-), floating patellar test in both knee joints (-), crepitus sensation in both knee joints (+). The tongue was enlarged and light red, without exfoliative coating. The tongue coating was thin and slightly greasy, accompanied by a wiry and slippery pulse. The VAS score for knee joint pain was 2 points, and the WOMAC score was 21 points. The Hp DOB value was 0.5 upon re-examination. The patient subsequently underwent intermittent treatment with a modified prescription for consolidation and resumed normal activities. No recurrence was observed during the one-year follow-up period.

Note: This case exemplifies the conventional "stomach and knee joint treatment". Imaging studies revealed that the extent of knee joint injury in the patient was notably more advanced and severe compared to peers of the same age group, which may be associated with the patient's chronic gastritis and Hp positivity. The administration of triple antibiotic therapy was intended to reduce systemic inflammation by eradicating Hp in the stomach, thereby alleviating joint inflammation and decelerating joint damage. Based on the patient's symptoms, clinical signs, and tongue and pulse diagnosis, the TCM diagnosis identified damp-heat in the spleen and stomach, with pathogenic factors contributing to knee pain. The combination of Wuling Powder and Juanbi Decoction, along with modified treatments, was employed to warm yang, eliminate dampness, clear heat, and alleviate arthralgia. This approach aligns with the TCM theory of "combined bi of body constituents and zang organs", which posits that in treating knee arthralgia, it is essential not only to address the knee itself but also to regulate Yangming. If the spleen and stomach are not properly regulated when treating arthralgia, and wind-inducing herbs are used indiscriminately, the condition may worsen, as noted by Yu Jiayan of the Qing Dynasty in *Yi Men Fa Lu* (*Principles and Prohibitions of Medical Profession*). This case employed an integrative approach combining traditional Chinese and Western medicine to treat both the stomach and knees. The treatment not only eradicated Hp but also eliminated dampness and alleviated arthralgia, addressing both the symptoms and underlying causes simultaneously, thereby achieving favorable outcomes.

5 Discussion

OA is a chronic joint disorder characterized by degenerative changes in the articular cartilage, alterations in the subchondral bone, formation of osteophytes at the joint margins, synovial lesions, and contracture of the joint capsule. Clinically, OA presents with symptoms such as joint pain, deformity, and functional impairment[36]. Prevention remains the most effective approach for managing OA[37]. KOA is the most prevalent form of OA, with a symptomatic KOA prevalence rate of 8.1% in China[36]. According to the *Clinical Diagnosis and Treatment Terms of Traditional Chinese Medicine*, issued by the State Administration of Traditional Chinese Medicine in 1997, KOA is classified as "knee arthralgia". The primary etiology and pathogenesis are attributed to insufficiency of the liver and kidneys, as well as damp-heat obstruction of the patella. This syndrome is characterized by a deficiency of the root and an excess of symptoms, as well as primary atrophy

and secondary obstruction[38]. Approximately 40% of KOA patients are infected with Hp[13-14], and the majority of gastritis patients with Hp infection exhibit damp-heat syndrome of the spleen and stomach[39-40].

According to TCM, the knee joint is nourished by the qi and blood of the stomach meridian. Deficiencies in the stomach and its associated meridians, or the presence of damp-heat in the spleen and stomach, can impair the functional integrity of the knee joint[41]. The stomach is situated in the middle energizer of the human body and corresponds anatomically to the knee joint located in the middle segment of the limb. The foot Yangming stomach meridian and the knee joint together form an integrated internal-external system network, consistent with the theory of the "combined bi of body constituents and zang organs". This study proposes a "gut-knee axis" model that spans "individual organs and limbs", grounded in the theoretical framework of the "combined bi of body constituents and zang organs".

A meta-analysis presented in the article confirmed that gastric Hp infection contributes to the onset and pathological progression of KOA via the "stomach-knee axis". The co-treatment drug targeting both "gastritis and arthritis" exhibits anti-inflammatory and antioxidant properties. This medication can eradicate Hp infection while simultaneously reducing joint and systemic inflammation, preserving the homeostasis of articular cartilage and the extracellular matrix of chondrocytes, and decreasing osteoclast formation. Hp infection is an intervenable risk factor in the onset and progression of KOA. Therapeutic strategies targeting "stomach and knee joint treatment" alleviate KOA-related damage by modulating the "stomach-knee axis" and eradicating Hp infection in the stomach. Clinical evidence indicates that prevention and treatment of Hp infection should be prioritized in patients with KOA. Integrating the assessment of gastric function associated with Hp infection into the routine diagnostic and therapeutic protocols for KOA, along with Hp eradication, is anticipated to enhance the clinical outcomes of KOA management.

Although there are currently limited in-depth studies examining the relationship between gastric Hp infection and KOA, this topic has garnered clinical interest. Future research should focus on designing both clinical and experimental studies to elucidate the actual association and underlying pathological mechanisms linking gastric Hp infection to KOA. Such investigations aim to offer novel insights and strategies for the prevention and treatment of OA, potentially through the eradication of Hp.

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