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Research Progress in Clinical Study of Chronic Constipation

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Abstract: ***Chronic constipation is a global functional gastrointestinal disorder with a prevalence of approximately 10% to 15%, significantly impacting patients' quality of life and imposing a substantial economic burden. In the past five years (2019-2024), significant progress has been made in this field regarding epidemiology, pathophysiology, diagnostic criteria, and treatment strategies. This article systematically reviews the research progress on chronic constipation using a four-dimensional analytical framework: "epidemiological characteristics—pathophysiological mechanisms—evolution of diagnostic criteria—comparison of treatment strategies. " In terms of epidemiology, new evidence has emerged regarding the dose-response relationship between dietary carotenoid and micronutrient intake and the risk of constipation. Regarding pathological mechanisms, research on the dysregulation of the gut microbiota-motility axis and the brain-gut axis has revealed multi-level progressive pathogenic mechanisms. In diagnosis, the promotion of Rome IV criteria and the application of novel bedside assessment tools such as portable ultrasound have driven the standardization of diagnostic processes. In treatment, new drugs such as prokinetics, secretagogues, and bile acid transporter inhibitors, along with non-pharmacological interventions like probiotics, biofeedback, and fecal microbiota transplantation, form a complementary treatment landscape. However, the strength of evidence varies across dimensions, and the translation from mechanisms to clinical practice remains a bottleneck. Precise subtyping and comprehensive intervention are the core directions for the future.***

Keywords: Chronic Constipation, Pathophysiological Mechanisms, Rome IV Criteria, 5-HT4 Receptor Agonists, Gut Microbiota, Biofeedback Therapy, Brain-Gut Axis.

1. Introduction

Chronic constipation is a common functional gastrointestinal disorder characterized by reduced stool frequency, hard stools, and/or difficult defecation, with a global prevalence of approximately 10% to 15% [1]. It significantly impacts patients' quality of life and imposes a heavy medical and economic burden. The pathogenesis of this disease is complex, involving multi-level factors such as enteric nervous system dysfunction, gut microbiota dysbiosis, and dysregulation of the brain-gut axis. Its clinical manifestations are highly heterogeneous, posing continuous challenges for clinical diagnosis and treatment [2].

In the past five years (2019-2024), significant progress has been made in multiple dimensions of chronic constipation research: epidemiological investigations have deepened from traditional descriptive studies to dose-response relationship analysis; pathophysiological mechanism research has expanded from single enteric neuropathy to the closed-loop regulatory network of the gut microbiota-brain-gut axis; diagnostic criteria have transitioned from Rome III to Rome IV, sparking discussions on clinical applicability; and treatment strategies have diversified from traditional laxatives to secretagogues, bile acid transporter inhibitors, and neuromodulation techniques, among others [3, 4].

This article systematically evaluates the research progress in chronic constipation over the past five years, using a four-dimensional analytical framework: "epidemiological characteristics—pathophysiological mechanisms—evolution of diagnostic criteria—comparison of treatment strategies, " with classic clinical guidelines and adult intervention reviews as baseline references [2, 4]. It aims to identify the distribution of evidence strength and applicable boundaries across various dimensions, providing a structured reference for clinical decision-making and basic research.

2. Epidemiological Characteristics and Risk Factors of Chronic Constipation

The prevalence of chronic constipation exhibits significant heterogeneity across gender, age, and geographical regions. Globally, the prevalence in women is approximately twice that in men, and it significantly increases with age [5]. Recent epidemiological studies over the past five years have further revealed complex associations between dietary factors, lifestyle factors, and the risk of constipation.

Regarding dietary factors, several large-scale cross-sectional studies based on the National Health and Nutrition Examination Survey (NHANES) database have provided new evidence. Wang et al. [6] analyzed NHANES 2005-2010 data and found a negative correlation between dietary carotenoid intake (including lycopene, α-carotene, and β-carotene) and constipation risk, with a dose-response effect. Yang et al. [7] further discovered a significant negative correlation between dietary live microbe intake and constipation risk, supporting the role of gut microbiota in constipation pathogenesis at a population level. Du et al. [8] focused on dietary copper intake and found a significant association between insufficient dietary copper intake and an increased risk of constipation, suggesting that micronutrients may play an important role in regulating gut motility. However, these studies were all cross-sectional in design, thus unable to establish causality, and self-reported dietary data bias is a methodological limitation that needs attention.

In terms of lifestyle factors, Yang et al. [5] utilized NHANES data to find that abnormal sleep duration (short and long sleep) was independently associated with an increased risk of constipation, and this association was more significant in

women. Furthermore, insufficient physical activity has also been confirmed by multiple studies as an independent risk factor for constipation [5, 9].

3. Pathophysiological Mechanisms of Chronic Constipation: Progression from Enteric Neuropathy to Brain-Gut Axis Dysregulation

The pathogenesis of chronic constipation exhibits multi-level progressive characteristics, with three interconnected layers forming a closed loop, collectively constituting a complementary space for therapeutic targets [10].

Layer 1—Structural lesions of the enteric nervous system (ENS) and Cajal interstitial cells (ICC)—forms the pathological basis. Studies indicate that patients with slow-transit constipation exhibit a significant reduction or destruction of the Cajal interstitial cell network in the colonic tissue, along with varying degrees of enteric neuron loss, leading to impaired pacing function of rhythmic colonic contractions. Abnormal 5-HT (5-hydroxytryptamine) signaling pathway is a key molecular link: 5-HT released by enterochromaffin cells promotes intestinal peristaltic reflexes by activating 5-HT4 receptors, while constipated patients often show abnormal 5-HT signal transduction. Liu et al. [11] confirmed through high-resolution colonic manometry that colonic dysmotility in patients with refractory constipation is closely related to autonomic nervous dysfunction, suggesting that ENS lesions do not exist in isolation but are linked with autonomic regulation.

Layer 2—Gut microbiota dysbiosis and short-chain fatty acid (SCFAs) metabolic abnormalities—drive intestinal motility disorders. The composition of gut microbiota in chronic constipation patients undergoes significant changes, characterized by a reduction in beneficial bacteria such as Bifidobacterium and Lactobacillus, and an increase in the relative abundance of pathogenic bacteria such as methanogens. This dysbiosis affects colonic motility through two pathways: first, decreased production of SCFAs (especially butyrate) weakens the energy supply to colonic smooth muscle and the stimulatory effect on 5-HT synthesis; second, abnormal bile acid metabolism alters the secretory-motor function of the colon. Misawa et al. [12] provided key evidence for the role of bile acid metabolism in constipation: the efficacy of elobixibat (a bile acid transporter inhibitor) was significantly correlated with fecal deoxycholic acid levels, suggesting that bile acid metabolism can serve as a biomarker for precision therapy.

Layer 3—Dysregulation of the brain-gut axis and autonomic nervous system—further amplifies colonic transit dysfunction. A systematic review by Ali et al. [13] showed that patients with functional gastrointestinal disorders generally exhibit reduced heart rate variability (HRV), reflecting autonomic nervous system imbalance. Abnormal secretion of brain-gut peptides (e.g., ghrelin, motilin) and central nervous system dysregulation of intestinal signals constitute the core of the central-peripheral linkage mechanism. Zhao et al. [14] further pointed out in their review that the regulatory network for intestinal motility, fluid, and electrolyte transport involves interactions among multiple systems, including nervous, endocrine, and immune systems, and the occurrence of constipation is a result of multi-node dysregulation within this network.

In the research of natural products and traditional Chinese medicine, multiple studies have explored the possibility of multi-target interventions. Platycodon grandiflorum polysaccharides improve constipation by regulating gut microbiota and colonic 5-HT levels [15]. Moringa oleifera Lam. leaf extract improves low-fiber diet-induced constipation through proteomics pathways [16]. Mulberry fruit exerts laxative effects by regulating gut microbiota [17]. These studies provide mechanistic support for the application of natural products in chronic constipation, but human validation is still insufficient.

4. Diagnostic Criteria and Assessment Methods for Chronic Constipation

In the past five years, the diagnosis of chronic constipation has transitioned from symptom-based diagnosis to an emphasis on objective assessment and standardized procedures. The release of the Rome IV criteria and its comparison with Rome III has been a central topic in the diagnostic field.

The Rome IV criteria made several key adjustments to the definition of functional constipation: simplifying the symptom duration from “at least 3 months within the last 6 months prior to diagnosis” to “the last 3 months prior to diagnosis, “ removing the “functional constipation” subtype, and clarifying the distinction between IBS-C and functional constipation. Russo et al. [18] compared the consistency of Rome III and Rome IV in diagnosing functional constipation in children, finding that while Rome IV criteria simplified the diagnostic process and improved diagnostic efficiency, it might lead to reclassification of some patients defined by Rome III, and there is controversy regarding the diagnostic consistency between the two standards. Heidelbaugh [19] pointed out from a primary care perspective that the simplification of Rome IV criteria facilitates preliminary screening by non-specialist physicians, but the identification of functional defecation disorders still requires specialized anorectal function tests.

Regarding anorectal function tests, balloon expulsion test combined with anorectal manometry is the first-line assessment method for functional defecation disorders. Sequential balloon expulsion tests can improve screening efficiency, but standardization and consistency among various tests still need improvement. From 2022 to 2024, multiple expert consensuses published standardized diagnostic procedures based on objective indicators, promoting the homogenization of diagnosis. Matsumoto et al. [20] and Mikessoku et al. [21] respectively proposed constipation diagnostic algorithms based on ultrasound examination of rectal fecal retention and constipation treatment algorithms based on ultrasound, providing objective assessment tools for patients who cannot subjectively report symptoms (e.g., those with cognitive impairment, disabled elderly, and palliative care patients). Yamamoto et al. [22] validated the feasibility of portable ultrasound devices in predicting rectal fecal

retention in palliative care settings, indicating that portable ultrasound and autonomic nervous function assessment, as non-invasive bedside tools, have the potential for rapid screening in primary care, but diagnostic accuracy and clinical promotion still depend on more prospective validation.

5. Pharmacological Treatment Strategies for Chronic Constipation

Pharmacological treatment strategies present a complementary three-category landscape, but head-to-head comparison data between drugs are limited, making it difficult to form clear stepped recommendations [3, 23].

The first category—traditional laxatives—remains the basic treatment. Osmotic laxatives (e.g., polyethylene glycol) are recommended as first-line choices due to their good safety and tolerability. Stimulant laxatives (e.g., bisacodyl, senna) have clear efficacy in short-term use, but the safety data for long-term use remain controversial, and individualized selection requires balancing efficacy and tolerability.

The second category—prokinetics—is represented by the 5-HT4 receptor agonist prucalopride. Bassotti [24] reviewed clinical evidence for prucalopride since 2015, confirming its clear prokinetic efficacy for patients with chronic idiopathic constipation unresponsive to traditional laxatives, with good cardiovascular safety. Pannemans et al. [3] further pointed out that the lack of head-to-head comparison data between prokinetics and secretagogues is a current bottleneck for evidence-based decision-making.

The third category—secretagogues and bile acid transporter inhibitors—represents a new direction based on gut microenvironment regulation. Linaclotide and lubiprostone improve constipation by increasing intestinal fluid secretion and have been proven effective in multiple clinical trials. Elobixibat promotes colonic peristalsis by inhibiting bile acid reabsorption and increasing colonic bile acid concentration; its efficacy is related to fecal deoxycholic acid levels [12], suggesting that bile acid metabolism can serve as a biomarker for precision therapy.

In terms of drug management for special populations, opioid-induced constipation (OIC) requires priority use of peripheral μ-opioid receptor antagonists (PAMORA). Kistemaker et al. [25] confirmed the effectiveness of PAMORA drugs in the prevention and treatment of OIC in cancer patients through a meta-analysis, providing high-quality evidence for clinical practice. Pharmacological treatment for neurogenic constipation (e.g., constipation associated with spinal cord injury, multiple sclerosis) needs individualized drug selection considering the characteristics of central nervous system diseases [26].

6. Non-pharmacological Treatments and Novel Interventional Strategies

Non-pharmacological interventions present a complementary layered approach, offering diverse treatment options for different subtypes of constipation patients.

Biofeedback therapy is a first-line non-pharmacological option for outlet obstruction constipation (dyssynergic defecation), with a growing trend towards home-based application. Xu et al. [28] demonstrated the high efficacy and safety of biofeedback therapy for dyssynergic defecation with a modified adaptive biofeedback training program, and the modified program helps reduce treatment costs and improve accessibility.

Probiotics and synbiotics show moderate evidence of efficacy in mild to moderate constipation, but strain-specific effects are significant. Van der Schoot et al. [27] conducted a systematic review and meta-analysis including multiple randomized controlled trials, finding that probiotics and synbiotics can significantly improve stool frequency and consistency in adult patients with chronic constipation, but efficacy varies greatly among different strains. Dimidi et al. [29] systematically elaborated on the mechanisms by which probiotics alleviate constipation, including regulating gut microbiota composition, increasing SCFA production, and improving the intestinal immune environment. Li et al. [30] found in animal studies that Lacticaseibacillus paracasei NCU-04 can simultaneously improve constipation and depressive-like behaviors induced by loperamide in mice through the microbiome-gut-brain axis, suggesting that specific strains may have dual physical and mental regulatory effects, but the lack of standardized formulations remains a major barrier to clinical application.

Fecal microbiota transplantation (FMT) and colonic electrical stimulation are emerging technologies with rich mechanistic research but limited clinical evidence. Yang et al. [31] found in a retrospective cohort study that FMT combined with biofeedback therapy was more effective than biofeedback alone for mixed constipation, but the long-term efficacy and safety of FMT still require validation. Ortega-Isasa et al. [32] explored the potential of colonic electrical stimulation to improve transit function by directly activating colonic smooth muscle and enteric neural pathways in a prospective review, but existing evidence is mainly based on case series and small-sample trials, lacking large-scale randomized controlled studies.

7. Research Gaps and Future Directions

There are three core research gaps in the current chronic constipation research.

First, mechanistic research is predominantly animal model-driven, with insufficient human validation. Although the three-tiered progressive mechanistic framework has been well-validated in animal experiments, the translation from animal models to human diseases still faces challenges. Research on the gut microbiota-motility axis is mostly based on correlational analysis using 16S rRNA sequencing and metabolomics, and the confirmation of causal mechanisms requires more interventional human studies.

Second, interventional studies lack head-to-head comparisons, making it difficult to formulate clear stepped treatment recommendations. Currently, efficacy evidence for pharmacological and non-pharmacological treatments mostly comes from placebo-controlled trials, and direct comparison

data between different drugs and different non-pharmacological interventions are extremely limited. This gap restricts clinicians' ability to make evidence-based decisions among multiple treatment options.

Third, the applicability of Rome IV diagnostic criteria in specific populations (e.g., elderly, children, cognitively impaired patients) still needs validation. Novel tools such as portable ultrasound and autonomic nervous function assessment, while offering the possibility of objective evaluation, lack large-scale prospective validation.

Future research should focus on the following directions: establishing interdisciplinary translational research pathways from gut microecology-neuromodulation to precision intervention, promoting multi-center head-to-head clinical trials to clarify the stepped sequence of treatments, and exploring precise phenotyping and comprehensive intervention strategies based on biomarkers (e.g., fecal bile acid profiles, HRV parameters).

8. Conclusion

In the past five years, the field of chronic constipation has made significant progress, ranging from epidemiological identification to molecular mechanism elucidation and diversified treatment strategies. Epidemiological research has revealed dose-response relationships between dietary factors and constipation risk. Pathophysiological mechanism research has constructed a three-tiered progressive framework from enteric neuropathy to brain-gut axis dysregulation. The transition of diagnostic criteria from Rome III to Rome IV has promoted the standardization of diagnostic processes. Pharmacological treatments have expanded from traditional laxatives to prokinetics, secretagogues, and bile acid transporter inhibitors, diversifying treatment directions. Non-pharmacological interventions have also achieved important advancements in biofeedback, probiotics, and emerging neuromodulation technologies.

However, the "epidemiological characteristics — pathophysiological mechanisms—evolution of diagnostic criteria — comparison of treatment strategies" four-dimensional analytical framework reveals that the strength of evidence varies across dimensions: epidemiological evidence is primarily based on cross-sectional studies, limiting causal inference; mechanistic research relies heavily on animal experiments with insufficient human validation; and interventional studies lack head-to-head comparisons, making it difficult to form clear stepped recommendations. The translation from mechanisms to clinical practice remains a bottleneck, and precise phenotyping and comprehensive intervention are core directions for future breakthroughs.

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