

Research Progress on the Correlation Between Chronic Ankle Instability and Mental Disorders

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Abstract

Objective: Chronic ankle instability (CAI) is the most common chronic complication after sprain of the lateral collateral ligament of the ankle, mainly characterized by repeated sprains, persistent pain and functional limitation, with 25% to 46% of patients developing CAI after a first sprain. This review aims to clarify the epidemiological characteristics, the possible bidirectional mechanisms, and the comprehensive intervention strategies linking CAI and mental disorders, so as to provide an evidence-based reference for the full management of CAI.

Methods: This is a systematic review of the literature on the correlation between CAI and mental disorders, covering the epidemiological characteristics of their comorbidity, the possible bidirectional pathogenic mechanisms (neuroplasticity, neurotransmitter imbalance, and fear-avoidance behavioral loops), and the evidence for clinical assessment and intervention.

Results: Existing cross-sectional studies consistently show that the comorbidity rates of anxiety and depression in patients with CAI are significantly higher than in healthy individuals. The two conditions reinforce each other through neuroplastic reorganization, neurotransmitter imbalance, and fear-avoidance behavioral loops, forming a vicious cycle of pain-psychological disorders-functional degradation. The correlation evidence is relatively sufficient, but the causal direction remains unclear, and some prevalence data derive from surgical subgroups and should not be directly generalized to all CAI patients.

Discussion: Integrating mental health screening into the routine management of CAI and providing multidisciplinary collaborative intervention for screen-positive patients is a feasible and theoretically sound strategy. However, the existing evidence is mainly observational in design. Prospective cohort and interventional studies are needed to clarify the causal direction and verify the efficacy of psychological interventions, so as to advance a framework of managing CAI with equal emphasis on physical and mental health and its clinical translation.

Keywords: chronic ankle instability; anxiety; depression; comorbid mechanisms; fear avoidance; neuroplasticity; comprehensive intervention

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Introduction

Lateral collateral ligament sprains of the ankle are one of the most common musculoskeletal injuries in sports medicine. According to the 2016 consensus statement of the International Ankle Consortium (IAC), its annual incidence rate is approximately 2.15 times per 1,000 people, especially among ball athletes^[1]. The proportion of patients who develop chronic ankle instability (CAI) after the first sprain is reported differently in various studies, and systematic reviews show that it is approximately 25% to 46%^[2,3]. Patients with CAI have long suffered from ankle joint pain, instability, and limitations in daily activities, and increasing evidence suggests that physical dysfunction and mental health problems often occur simultaneously and aggravate each other^[4,5].

Before delving into this comorbidity phenomenon, it is necessary to clarify two methodological premises: (1) most existing studies are cross-sectional or retrospective designs, revealing statistical correlations rather than causal relationships, and the two should not be confused; (2) some study subjects are patients who have undergone foot and ankle surgery. Nixon et al.^[6] found that those with higher preoperative Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety scores experienced more severe postoperative pain and less functional improvement, suggesting that mental state has an independent impact on surgical prognosis, but surgical subgroup data cannot directly represent the baseline level of mental disorders in the non-surgical CAI population. Based on the above premises, a deeper understanding of the comorbidity patterns of CAI and mental disorders and their possible mechanisms is of great significance for developing more targeted clinical management strategies. This review aims to provide clinical management strategies for the comorbidity of CAI and mental disorders and to provide theoretical support for future mechanistic and interventional studies on this comorbidity.

Definition, diagnostic criteria, epidemiological characteristics, and pathogenesis of chronic ankle instability

CAI is a clinical syndrome characterized by persistent instability or recurrent sprains in the ankle joint for more

than 12 months following one or more lateral collateral ligament sprains. The selection criteria established by the IAC define CAI as follows: (1) a history of ankle sprain with the first injury occurring at least 12 months ago; (2) recurrent instability or loss of balance in the ankle; and (3) functional limitation (Cumberland Ankle Instability Tool [CAIT] ≤ 24 points)^[7]. Based on the dominant mechanism, CAI can be divided into mechanical instability, which is mainly caused by anatomical structural damage, and functional instability, which is mainly caused by neuromuscular control abnormalities. Both often coexist in clinical practice^[8].

CAI is most common in adolescents and young adult athletes. Regarding gender differences, the overall incidence rate is slightly higher in women than in men, which may be related to the anatomical characteristics of the ankle joint, the degree of ligament laxity, and hormone levels^[3]. In terms of sports, basketball, football, volleyball, and other sports that require frequent changes of direction and jumping landings have the highest risk^[1]. It should be noted that the prevalence of mental disorders in CAI patients varies greatly in different studies (14% to 50% for anxiety, 10% to 55% for depression), which is mainly related to differences in study populations (community, outpatient, surgery candidates), assessment tools, and diagnostic thresholds. Caution is required when interpreting^[4,6].

The pathogenesis of CAI involves multiple levels. The current mainstream framework is the updated model proposed by Hertel and Corbett in 2019^[8], which integrates the three dimensions of neuromusculoskeletal dysfunction, histopathological changes, and patient subjective perception. Ligament structural damage is the material basis of mechanical instability, with the anterior talofibular ligament and calcaneofibular ligament being the most susceptible. Proprioceptor damage leads to decreased joint position sense and delayed neuromuscular reflexes, which is the core mechanism of functional instability. In recent years, neuroimaging evidence has further suggested that persistent pain can drive plastic remodeling of the central nervous system, manifested in abnormal sensorimotor cortex activation patterns and changes in functional connections, providing a neurobiological basis for understanding the comorbidity of CAI and mental disorders^[9,10].

Research progress on CAI and mental disorders

Anxiety and depression

Anxiety disorders and depressive disorders are the most commonly reported types of mental disorders in the CAI population. A cross-sectional study by Suttmilller et al.^[4] found that post-injury fear, perceived instability, and pain intensity jointly predict the degree of functional limitation, and the predictive power of psychological factors is no less than that of physical examination indicators. Yu et al.^[5] confirmed through multifactor regression analysis in 2025 that the severity of anxiety and depression is independently and negatively related to the Foot and Ankle Outcome Score (FAOS). This association is still significant after controlling for pain intensity, suggesting that the adverse effects of mental disorders on function are not entirely mediated by pain. It should be noted that the above-mentioned studies are all cross-sectional designs and reveal cross-sectional associations. There are no prospective cohort studies to clarify the temporal sequence between anxiety/depression and CAI.

The systematic review by Bain et al.^[11] included literature on ankle sprain history and found that individuals with a history of repeated ankle sprains had higher levels of functional impairment in dimensions such as fear of movement, mental health scores, and self-efficacy than healthy controls. This pattern of psychological damage is closely related to the persistence of CAI. The meta-analysis by Powden et al.^[12] further showed that conservative rehabilitation training for CAI not only improves physical function, but also simultaneously improves patients' health-related quality of life (HRQoL), suggesting the possibility of coordinated recovery of mental state and physical function.

Movement fear and fear avoidance beliefs

Kinesiophobia and fear-avoidance beliefs are a special type of psychological reaction in CAI patients, with an incidence rate of approximately 30% to 60%. A cross-sectional study by Alshahrani and Reddy^[13] showed that the degree of fear of movement (Tampa Scale of Kinesiophobia [TSK] score) was significantly

correlated with decreased ankle proprioception and static balance ability (r ranged from -0.58 to -0.42 , $p < 0.05$). A systematic review by Suttmilller and McCann et al.^[14] showed that self-reported post-injury fear scores were significantly higher in patients with CAI compared with healthy controls, and the difference persisted after controlling for injury severity. The clinical significance of the fear avoidance mechanism is that patients may accelerate the degeneration of neuromuscular function of the ankle joint by reducing active activities, but this hypothesis currently lacks direct verification by longitudinal studies.

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is also detected in patients with a history of severe ankle trauma (combined with fractures, dislocations, or requiring emergency surgery). A systematic review and meta-analysis of six studies by Muscatelli et al.^[15] showed that the weighted combined prevalence of PTSD after acute orthopedic injury was approximately 16.8%, and the prevalence of depression was approximately 27%. The severity of injury, the degree of pain, and a history of psychiatric illness were the main risk factors. In the CAI population, which usually does not have severe bone injury, the incidence of PTSD may be much lower than the above estimate, and related special studies are still lacking.

Possible mechanisms of interaction between CAI and mental disorders

Recent studies have shown that there is a bidirectional pathological mechanism of interaction between CAI and mental disorders. Its intrinsic pathways mainly involve three core aspects: (1) abnormal neuroplasticity and central sensitization; (2) neurotransmitter imbalance; (3) the vicious cycle of fear avoidance behavior. First, persistent pain can cause plasticity reorganization of the central nervous system. Many imaging studies have confirmed this central remodeling feature. Among them, the functional near-infrared spectroscopy (fNIRS) study found that CAI patients had increased activation area and decreased efficiency of sensorimotor cortex in the single-leg standing task, suggesting that there is compensatory recruitment of the central nervous system for ankle joint control^[10]. On this basis, a study combining large sample data from the UK Biobank with clinical

validation further found that there was abnormal reorganization of functional connectivity between brain regions related to pain processing (insula, anterior cingulate cortex) and motor control areas in CAI patients, and this change was positively correlated with anxiety self-rating score ($r = 0.31$, $p < 0.01$), suggesting that neural plasticity driven by chronic ankle pain may increase the susceptibility of emotion regulation network^[9]. In 2025, a structural neuroimaging study further supplemented the relevant evidence from the anatomical structure level. This study found that the change in gray matter density of the insular cortex in CAI patients was significantly correlated with the degree of pain-related fear ($r = 0.43$, $p < 0.05$), providing direct structural evidence for the neuroplasticity-fear comorbidity hypothesis^[16]. It is worth noting that the effects of the two are not unidirectional physical lesions inducing emotional abnormalities. The reverse effect from mental disorders to CAI also has a clear biological basis. In states of anxiety and depression, the hypothalamic-pituitary-adrenal axis is activated, and cortisol levels continue to increase, which can reduce the pain threshold of the nociceptive system and make patients more sensitive to ankle pain stimulation, ultimately forming a two-way reinforcing cycle in which physical injury and emotional abnormalities promote each other^[17]. In addition to the remodeling of central structure and function, neurotransmitter disorders are also an important biochemical mechanism mediating the co-morbidity of the two. Monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT) and norepinephrine play an important role in pain modulation and emotion regulation. In long-term chronic pain conditions, the function of the descending inhibitory system of the spinal cord and brainstem is weakened, and the levels of monoamine transmitters are reduced, which can intensify pain perception. Hyperalgesia can also induce depressive mood^[17]. This mechanism also reasonably explains the dual benefits of selective 5-HT reuptake inhibitors (SSRIs) for some patients with chronic musculoskeletal pain and depression, both analgesic and anti-emotional abnormalities. However, there are currently no randomized controlled trials (RCTs) of drug intervention specifically targeting the comorbidity of CAI-depression, and there is still a gap in relevant drug treatment evidence. Beyond biological mechanisms, psychological and behavioral abnormalities further link and amplify the comorbid damage of the body and mind.

Among them, the fear-avoidance model is a mature theoretical framework for explaining this behavioral pathway. The catastrophizing cognition of pain and fear of re-injury after ankle injury drives patients to actively reduce limb activity, which in turn leads to decreased ankle muscle strength, proprioceptive degeneration, and joint stiffness, objectively increasing the risk of re-sprain. At the same time, the social reduction and decreased self-efficacy caused by limited activity will further aggravate anxiety and depression, forming a closed-loop vicious cycle^[13,14]. The systematic review by Wertli et al.^[18] also confirms this pattern. Their study shows that fear-avoidance belief is an independent predictor of functional disability and poor prognosis in patients with chronic musculoskeletal pain. However, the efficacy research on psychological interventions is still incomplete at present. Whether interventions on fear-avoidance belief (such as graded exposure therapy) can simultaneously improve ankle function still needs to be tested by a specific RCT for the CAI population. Although basic research and various observational studies have preliminarily clarified the multidimensional potential mechanisms of comorbidity between CAI and mental disorders, significant research limitations remain. It should be noted that all the aforementioned mechanisms are proposed based on cross-sectional association studies and basic experimental deductions. Currently, there are no high-quality causal inference studies that directly manipulate specific mechanisms and observe comorbid outcomes, making it impossible to definitively confirm the dominant role of each pathway and the causal sequence relationship. Further high-quality clinical research is needed to further verify the causal relationship between chronic ankle instability and mental disorders, and the specific regulatory mechanisms between the two.

Impact of CAI combined with mental disorders on patient outcomes

Current clinical research confirms that CAI combined with mental disorders is not simply a physical illness superimposed with psychological problems. The two interact and influence each other, comprehensively impairing the patient's overall health status from multiple levels, including quality of life, rehabilitation adherence and long-term prognosis, and social functioning, signifi-

cantly increasing the complexity of disease diagnosis, treatment, and rehabilitation. In terms of quality of life, patients with CAI and mental disorders had significantly lower HRQoL scores in all three dimensions of physical function, psychological function, and social function compared to patients with CAI alone. Among them, Houston et al.^[19] showed that, compared with healthy controls, CAI patients scored significantly lower on the Foot and Ankle Ability Measure (FAAM) and its Sports subscale (FAAM-Sport), Foot and Ankle Outcome Score (FAOS), and physical activity scale. The scores of all dimensions of the ankle joint scale were significantly reduced, and the scores of the motor dysfunction scale (Tampa scale score) were higher than those of the control group, suggesting that mental disorders have an independent adverse effect on quality of life. Treatment targeting the ankle joint itself may not be sufficient to achieve a satisfactory overall outcome for such patients. At the same time, population stratification studies have further supplemented the relevant conclusions. Kosik et al.^[20] found in their study of middle-aged CAI patients that, compared with ankle copers and uninjured control groups, CAI patients had significantly lower scores on both the physical and psychological dimensions of the PROMIS overall health scale, and this gap was more prominent in the middle-aged group than in younger athletes, suggesting that the impact of CAI on quality of life may increase with age. In addition to the overall decline in quality of life, coexisting mental disorders can also interfere with the entire rehabilitation process and hinder long-term functional recovery from multiple dimensions. The mechanism by which mental disorders affect the rehabilitation process is multidimensional: anxiety can reduce patients' confidence and compliance with the rehabilitation plan; depression directly impairs motivation, cognitive flexibility and self-management ability. A study by Nakagawa et al.^[21] on patients with chronic foot and ankle diseases found that patients with anxiety or depression had significantly worse Visual Analogue Scale pain scores and scores on each subscale of the Self-Administered Foot Evaluation Questionnaire scale than patients without mental disorders, suggesting that emotional disorders indirectly hinder functional recovery by amplifying pain perception. A study by Nixon et al.^[6] further showed that patients with higher preoperative PROMIS anxiety scores in foot and ankle surgery had significantly worse postoperative pain and functional

improvement than the low-anxiety group. However, this conclusion comes from the surgical subgroup and needs further confirmation for its application to non-surgical CAI patients. Under the combined effect of physical function and psychological state, patients' social function will also be significantly impaired. Long-term functional limitation and psychological disorders together lead to reduced social participation and decreased occupational performance. Arnold et al.^[22] found in their study of patients with functional ankle instability that the degree of ankle instability was negatively correlated with the multidimensional score of health-related quality of life. Physical function limitation indirectly aggravates patients' social alienation and psychological burden by restricting daily activities and sports participation. The causal path is still unclear. It is worth noting that social function impairment itself may also aggravate mental disorders, forming a closed loop, suggesting that clinical intervention should pay attention to patients' occupational status and social support network at the same time. In general, physical injury, psychological disorders and social function impairment are mutually causal and form a vicious cycle, which seriously damages patients' normal social life and occupational status, and also puts forward new requirements for comprehensive clinical intervention.

Clinical assessment and intervention recommendations for CAI and mental disorders

Clinical assessment recommendations for comorbid CAI and mental disorders

The diagnosis and functional assessment of CAI should follow the multidimensional framework recommended by the IAC^[7]: (1) medical history inquiry (number of sprains, duration, functional limitations); (2) ligament stability examination (anterior drawer test, talus tilt test, combined with stress position X-ray confirmation if positive); (3) neuromuscular function assessment (balance test, muscle strength test); (4) patient-reported outcomes (CAIT, FAAM, FAOS scale). Magnetic resonance imaging and ultrasound have complementary value when concomitant cartilage or tendon injury is suspected, but are not recommended as routine examinations for all patients with CAI^[23]. In view of the high comorbidity rate of anxiety and depression in patients with CAI, it is

recommended to routinely use validated self-report tools for screening at initial and follow-up visits, including the Generalized Anxiety Scale (GAD-7), Patient Health Questionnaire (PHQ-9), and TSK-11. Those who screen positive ($GAD-7 \geq 5$ or $PHQ-9 \geq 5$) should be further evaluated by a specialist using the Hamilton Anxiety/Depression Rating Scale, or be referred to a psychiatry or clinical psychology department^[5]. Currently, there is no international consensus on the specific psychological screening process for CAI. The above recommendations are based on general recommendations for chronic musculoskeletal pain and still need to be specifically verified for the CAI population. However, the main limitation of the current assessment system is that mental disorder assessment and motor function assessment are often completed separately by different specialists at different time points, lacking integration. In addition, there are few studies on the measurement equivalence (measurement invariance) of the existing Chinese version of the scale in specific CAI populations. When using it cross-culturally, attention should be paid to localized reliability and validity verification.

Treatment strategies for comorbid CAI and mental disorders

Recent studies have shown that in terms of somatic treatment for CAI, conservative treatment is the first-line option for the vast majority of CAI patients. The intervention with the most sufficient evidence-based support is neuromuscular training (proprioceptive training, balance training), and multiple systematic reviews have consistently reported that it can significantly reduce the risk of reinjury (relative risk = 0.37–0.59)^[2]. The randomized controlled trial by Bleakley et al.^[24] also showed that using an accelerated rehabilitation program after ankle sprain can restore function faster, providing a basis for early active intervention. Orthopedic ankle braces and kinesiology tape have preventive value in high-risk sports scenarios. Nonsteroidal anti-inflammatory drugs are mainly used to control symptoms in the acute inflammatory phase and are not used as a long-term management method for CAI^[23]. For patients with severe mechanical instability who have failed conservative treatment for 3 to 6 months, surgical repair is a reasonable choice; the 5-year follow-up study by Guelfi et al.^[25] showed that the clinical outcomes of arthroscopic all-

inside ligament repair are equivalent to or even better than open repair, and it has the advantage of being minimally invasive. However, head-to-head high-quality RCTs between the two and simple conservative treatment still need to be carried out. Psychological and pharmacological treatments for mental disorders: Cognitive behavioral therapy (CBT) is the first-line psychological intervention for chronic musculoskeletal pain and comorbid anxiety/depression. The systematic review and meta-analysis by Liu et al.^[26] included multiple RCTs and confirmed that CBT can significantly reduce pain intensity and psychological distress in patients with chronic musculoskeletal pain, and improve functional status. It should be pointed out that the above evidence mainly comes from people with chronic low back pain and osteoarthritis. Randomized controlled studies of CBT specifically for CAI combined with anxiety/depression are still blank, and it is uncertain whether the effect size can be transferred directly. For patients with moderate to severe anxiety/depression, the use of SSRI drugs under the supervision of a psychiatrist is a reasonable choice^[17]; for those with sleep disorders, cognitive behavioral insomnia treatment can help break the closed loop of sleep disorder-hyperalgesia-anxiety exacerbation. Given the bidirectional interactive nature of CAI and mental disorders, single-disciplinary intervention is often insufficient to achieve optimal outcomes. The multi-disciplinary team (MDT) integrates orthopedics/sports medicine, rehabilitation medicine, clinical psychology and psychiatry, and can simultaneously develop individualized plans for both physical and psychological dimensions. Evidence in the field of chronic musculoskeletal pain shows that combining physical therapy with psychological intervention such as CBT can further improve pain intensity and functional outcomes^[26]. However, there has been no report on the MDT model RCT targeting CAI-mental disorder comorbidity. Standardization of assessment nodes (such as mandatory psychological screening before surgery and before discharge) and standardization of the referral process are the first steps to advance the MDT model. However, current research on CAI and mental disorders still has certain systemic limitations: (1) unclear causal direction—most studies are cross-sectional or retrospective designs, making it impossible to confirm whether mental disorders are an antecedent, consequence, or a concomitant result of common third factors (such as reduced physical

activity and social isolation); (2) insufficient sample representativeness—a considerable portion of mental disorder prevalence data comes from surgical subgroups and cannot be directly generalized to the community CAI population; (3) heterogeneity of assessment tools—different studies use different scales and diagnostic thresholds, and heterogeneity needs to be carefully handled in meta-analysis; (4) inadequate confounding control—confounding factors such as age, gender, pain intensity, and degree of functional limitation are not adequately controlled in most studies.

Based on the above limitations, future research should prioritize addressing the following issues: (1) conducting a prospective cohort study on patients with first-time ankle sprains, tracking their mental health status at 3, 6, 12, and 24 months post-injury to clarify the chronological order of comorbidities and risk predictors; (2) designing CBT or graded exposure therapy RCTs for patients with CAI and anxiety/depression to test whether psychological intervention can independently improve ankle function; (3) using neuroimaging (functional magnetic resonance imaging, fNIRS) and biomarkers (cortisol, inflammatory factors) to track the dynamic relationship between CAI neuroplasticity changes and mental symptoms; (4) conducting a study on the implementation of a standardized pathway for CAI psychological screening in a multidisciplinary treatment setting to assess its impact on referral rates and patient outcomes.

Conclusion

In summary, existing observational evidence consistently indicates that the detection rate of anxiety and depression in CAI patients is significantly higher than in healthy individuals, and the two reinforce each other through three dimensions: altered neuroplasticity, fear-avoidance behavioral loops, and neurotransmitter imbalance. However, the causal strength of both CAI leading to mental disorders and mental disorders exacerbating CAI cannot be confirmed with existing data—this is the core methodological challenge in this field and a key bottleneck restricting the development of clinical guidelines. At present, integrating mental health screening into the routine management process of CAI and providing multidisciplinary collaborative intervention for screening-positive patients is a feasible and theoretically sound

strategy, but its effectiveness still needs to be verified by high-quality intervention studies. This review aims to promote clinicians' understanding of the concept of managing CAI with equal emphasis on physical and mental health, and to provide a literature basis for future mechanistic and interventional studies on this comorbidity.

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Authors' contributions

Panyue Wei and Tingting Gao contributed equally to this article. Panyue Wei and Tingting Gao conceived the study and drafted the manuscript. Pei Chen and Panjin Wei searched the literature and reviewed the manuscript. Dawei Ju conceived and supervised the study, provided resources, and revised the manuscript. All authors reviewed, edited, and approved the final version of the manuscript and agree to its publication.

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The authors used GPT-4 as a language-editing tool to improve grammar, clarity, and readability. The AI tool was not used for data analysis, data generation, image processing, or scientific content creation. All outputs were carefully reviewed and verified by the authors, who take full responsibility for the final content.

Competing interests

The authors declare no conflicts of interest.

Consent for publication

All the authors consent to the publication of identifiable

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Data availability statement

No datasets were generated or analyzed for this work.

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