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Editorial

Chronic systemic inflammation: A common pathway linking chronic diseases

Inflammation is a fundamental biological response that preserves tissue homeostasis following infection, injury, or exposure to harmful stimuli, including pathogens, damaged cells, and irritants. Under physiological conditions, acute inflammation is tightly regulated and self-limiting, leading to elimination of the offending agent and restoration of tissue integrity. However, when the triggering stimulus persists or the mechanisms responsible for resolution fail, inflammation may evolve into a chronic, low-grade systemic process. Several factors promote chronic low-grade inflammation, including aging, smoking, unhealthy diet, physical inactivity, obesity, hormonal changes, psychological stress, and inadequate sleep (1, 2).

Increasing evidence indicates that chronic systemic inflammation (CSI) may be both a consequence and a driver of chronic disease. Although it often develops secondary to conditions such as obesity, autoimmune diseases, or persistent infections, once established it may become a self-perpetuating process that contributes to the initiation, progression, and complications of numerous chronic disorders, including cardiovascular disease, diabetes mellitus, chronic kidney disease, metabolic dysfunction-associated steatotic liver disease, osteoarthritis, neurodegenerative diseases, and cancer (1, 3-5).

Unlike acute inflammation, chronic low-grade inflammation is often clinically silent. Patients usually do not exhibit classical inflammatory manifestations such as fever, severe pain, or overt functional impairment. Instead, a persistent subclinical inflammatory state develops, characterized by continuous activation of both innate and adaptive immune responses. Although relatively mild in intensity, this persistent inflammatory response may continue for years, gradually inducing cumulative tissue injury and functional decline (4).

Importantly, chronic low-grade systemic inflammation may arise from persistent localized inflammatory processes. Chronic conditions such as obesity, metabolic dysfunction-associated steatotic liver disease, Helicobacter pylori-associated gastritis, and periodontitis illustrate how persistent local inflammation can extend beyond the affected tissue and contribute to a chronic systemic inflammatory state. Although these conditions are frequently clinically silent or minimally symptomatic, they are associated with sustained release of inflammatory mediators, including TNF-α, IL-1β, and IL-6, leading to endothelial dysfunction, metabolic disturbances, oxidative stress, and progressive tissue injury that collectively promote the development and progression of multiple chronic diseases (4, 6).

Accumulating evidence indicates that cardiovascular disease, diabetes mellitus, chronic kidney disease, autoimmune disorders, neurodegenerative diseases, chronic lung disease, obesity, and cancer, although clinically distinct, share common inflammatory mechanisms. Persistent systemic inflammation may therefore represent both a consequence and a driving force of disease progression, establishing a vicious cycle in which inflammation promotes tissue injury while damaged tissues further amplify inflammatory responses (7).

The pathogenesis of CSI involves persistent activation of innate and adaptive immune responses through multiple interconnected inflammatory pathways. Infectious agents, tissue injury, metabolic abnormalities, environmental pollutants, psychological stress, and unhealthy lifestyle factors activate pattern-recognition receptors, resulting in sustained activation of intracellular signaling pathways, including nuclear factor-κB (NF-κB), mitogen-activated protein kinase (MAPK), and Janus kinase-signal transducer and activator of transcription (JAK-STAT). These pathways promote prolonged production of IL-1β, IL-6, TNF-α, and acute-phase proteins such as hs-CRP, ultimately leading to endothelial dysfunction, oxidative stress, mitochondrial injury, insulin resistance, extracellular matrix remodeling, impaired tissue repair, and progressive organ dysfunction (1, 8).

Additionally, numerous modifiable lifestyle and environmental factors, including physical inactivity, unhealthy dietary patterns, cigarette smoking, inadequate sleep, and exposure to environmental and industrial pollutants, promote a sustained inflammatory state, creating an inflammatory milieu that predisposes susceptible individuals to chronic disease. Consequently, chronic inflammation should be viewed not only as a biological phenomenon but also as a reflection of cumulative environmental, metabolic, and behavioral influences throughout life (9, 10).

The clinical implications of CSI extend across virtually every medical specialty. In cardiovascular medicine, chronic inflammation contributes to endothelial dysfunction, atherosclerotic plaque formation, plaque instability, thrombosis, and heart failure. In metabolic disorders, inflammatory cytokines impair insulin signaling and promote the development of type 2 diabetes mellitus and metabolic syndrome. In chronic kidney disease, persistent inflammation accelerates renal fibrosis and contributes to cardiovascular complications. Similarly, chronic inflammation may promote carcinogenesis by inducing DNA damage, stimulating angiogenesis, and facilitating tumor growth and metastasis.

In autoimmune diseases such as rheumatoid arthritis, persistent immune activation causes progressive tissue destruction while simultaneously increasing cardiovascular risk. Neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease, are also increasingly recognized to involve chronic neuroinflammation that contributes to neuronal dysfunction and cognitive decline. Aging itself has been associated with a persistent low-grade inflammatory state, commonly referred to as "inflammaging," which may partially explain the increased susceptibility of older adults to multiple chronic diseases (11, 12).

Reliable assessment of systemic inflammation remains an important clinical challenge. Among currently available biomarkers, high-sensitivity C-reactive protein has emerged as one of the most practical and extensively validated indicators of low-grade inflammation. Because hs-CRP can detect relatively small elevations in circulating CRP concentrations, it provides greater sensitivity than conventional CRP assays for identifying low-grade inflammatory activity. Elevated hs-CRP concentrations have been associated with increased risk of cardiovascular events, diabetes, chronic kidney disease progression, functional impairment, and mortality. Additional inflammatory biomarkers, including erythrocyte sedimentation rate (ESR), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), IL-6, TNF-α, and other cytokines, may provide complementary information regarding inflammatory status. Nevertheless, no single biomarker fully reflects the complexity of chronic systemic inflammation, and interpretation should always consider the patient's clinical condition and potential confounding factors (13-15).

Although chronic inflammation has no specific clinical manifestations of its own, the persistent inflammatory process may produce a range of nonspecific symptoms and functional impairments, including fatigue, chronic pain, reduced muscle strength, sarcopenia, impaired physical performance, and disability. These manifestations may occur in patients with diverse chronic diseases, including cardiovascular disease, chronic kidney disease, diabetes mellitus, osteoarthritis, and autoimmune disorders, and are often difficult to distinguish from symptoms attributable to the underlying disease itself.

Recognition of chronic inflammation is therefore clinically important, as persistent inflammation may contribute to symptom burden, delayed recovery, and poor functional outcomes beyond the primary disease process. This also has important implications for rehabilitation and functional recovery following acute illnesses. For example, in stroke survivors, chronic inflammation may delay neurological recovery, aggravate musculoskeletal symptoms, impair motor function, and reduce independence in activities of daily living. Similar inflammatory mechanisms may contribute to poorer outcomes in many other chronic disabling conditions.

However, the association between CSI and chronic diseases does not necessarily establish causality, and the extent to which inflammation represents a cause, consequence, or perpetuating factor may vary across diseases.

Despite their increasing incorporation into clinical research, inflammatory biomarkers remain underutilized in routine clinical practice. Future investigations should determine whether serial assessment of inflammatory markers can improve risk stratification, monitor disease activity, predict functional outcomes, or guide therapeutic interventions across diverse chronic diseases. In particular, further studies are needed to clarify the role of hs-CRP as an

accessible biomarker for identifying patients who may benefit from targeted anti-inflammatory strategies (16, 17).

Importantly, individuals with persistently elevated hs-CRP concentrations are at greater risk of adverse health outcomes, particularly cardiovascular events and the development or progression of several chronic diseases. However, hs-CRP should always be interpreted in the context of the patient's clinical condition and in the absence of acute infection or other transient causes of inflammation. Repeated measurements may provide a more reliable assessment of chronic systemic inflammation than a single determination.

Management of CSI requires a comprehensive strategy that targets both the underlying disease and modifiable inflammatory risk factors. Effective treatment of chronic inflammatory disorders, particularly autoimmune diseases, remains essential. In rheumatoid arthritis, sustained remission or low disease activity achieved with disease-modifying antirheumatic drugs and biologic agents, including TNF inhibitors and IL-6 inhibitors, is associated with lower hs-CRP concentrations, reduced systemic inflammation, improved long-term outcomes, and lower cardiovascular risk. Equally important are interventions targeting obesity, hypertension, diabetes mellitus, dyslipidemia, smoking, unhealthy dietary habits, physical inactivity, chronic psychological stress, and inadequate sleep. Regular exercise, weight reduction, adherence to healthy dietary patterns, smoking cessation, and adequate sleep all exert measurable anti-inflammatory effects (18).

Beyond lifestyle modification, several commonly used medications also possess clinically important anti-inflammatory properties. Statins reduce hs-CRP concentrations independently of lipid lowering, while colchicine suppresses inflammasome-mediated inflammation and reduces recurrent cardiovascular events in selected patients with atherosclerotic cardiovascular disease. Metformin not only improves insulin sensitivity but also attenuates systemic inflammatory pathways. Nevertheless, the clinical benefits of anti-inflammatory strategies may vary across diseases, and evidence from clinical trials has not been uniformly positive. Such heterogeneity highlights the complexity of systemic inflammatory pathways and the need for appropriate patient selection and more precisely targeted interventions. Therefore, treatment should primarily focus on identifying and correcting the underlying drivers of inflammation (19-21). Recent clinical trials further suggest that therapies targeting inflammatory pathways may reduce cardiovascular events independently of lipid lowering, while emerging approaches directed against the NLRP3 inflammasome, JAK-STAT signaling, and the gut microbiome may provide more precise therapeutic options in the future (2, 18, 19).

The recognition of CSI as a common biological denominator across numerous chronic diseases offers an opportunity to move beyond traditional organ-specific approaches toward a more integrated understanding of disease pathogenesis. Rather than viewing inflammation solely as a secondary consequence of disease, clinicians and researchers should consider CSI a potentially modifiable determinant of disease onset, progression, and clinical outcome. Such a paradigm encourages interdisciplinary collaboration and highlights the importance of preventive strategies aimed at reducing the cumulative inflammatory burden throughout life (19).

In conclusion, chronic systemic inflammation represents a unifying mechanism linking many of today's most prevalent chronic diseases. Although considerable progress has been made in elucidating its molecular pathways, important questions remain regarding optimal biomarkers, individualized risk assessment, and targeted therapeutic interventions. Future research should focus on identifying clinically applicable inflammatory biomarkers, validating anti-inflammatory treatment strategies, and determining whether reducing chronic inflammatory burden translates into meaningful improvements in morbidity, functional capacity, quality of life, and survival. Recognition, early identification, and effective management of chronic systemic inflammation may ultimately become central components of precision medicine and preventive healthcare.

Key words: Chronic, inflammation, diseases

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