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LOW-GRADE INFLAMMATION IN MODERN CIVILIZATION DISEASES: A NARRATIVE REVIEW OF MECHANISMS, BIOMARKERS, AND CLINICAL IMPLICATIONS

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ABSTRACT

Over the last century, the epidemiological landscape has shifted from acute infectious diseases to chronic non-communicable diseases (NCDs), including cardiovascular disease, type 2 diabetes, and neurodegeneration. These pathologies share a common, underlying biological substrate: chronic, low-grade inflammation, which is hypothesized to arise from an evolutionary mismatch between the human genome and the modern anthropogenic environment. This narrative review synthesizes evidence regarding the molecular mechanisms of sterile inflammation, emerging biomarkers, and therapeutic interventions by integrating data from immunology, metabolic medicine, and large-scale clinical trials. The analysis demonstrates that the pathology is driven by triggers such as metabolic surplus and oxidative stress, which activate the NLRP3 inflammasome and NF-κB pathways. This activation leads to reciprocal dysfunction between insulin signaling and endothelial integrity, creating a metabolic-vascular nexus that drives atherosclerosis, while gut dysbiosis and blood-brain barrier disruption extend this inflammation to the central nervous system, promoting neurodegeneration. While high-sensitivity CRP remains the standard biomarker, emerging markers like suPAR and GlycA offer superior stability and prognostic value. Therapeutically, the CANTOS and LoDoCo2 trials have validated the efficacy of targeting specific inflammatory pathways (IL-1β, NLRP3) over broad immunosuppression. Ultimately, low-grade inflammation is identified as the defining physiological signature of the modern age, serving as the "common soil" for multimorbidity. Effective management necessitates the adoption of a Personalized Immunometabolism framework, integrating biomarker-guided pharmacotherapy (e.g., colchicine) with lifestyle interventions that resolve the fundamental evolutionary mismatch, as future progress depends on bridging the gap between prognostic biomarkers and actionable clinical protocols.

KEYWORDS

Low-grade Inflammation, NLRP3 Inflammasome, Evolutionary Mismatch, Biomarkers, suPAR, Colchicine, Immunometabolism

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Introduction

The trajectory of human health over the last century is characterized by a profound epidemiological transition. While advancements in sanitation, vaccination, and antibiotics have dramatically curtailed the threat of acute infectious diseases, a new class of pathologies has risen to prominence. These conditions, collectively termed non-communicable diseases (NCDs) or "civilization diseases," include cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), obesity, non-alcoholic fatty liver disease (NAFLD), neurodegenerative disorders, and certain malignancies [1]. Although phenotypically distinct, these pathologies share a common, underlying biological substrate: a state of chronic, low-grade, non-resolving inflammation [2, 3].

Inflammation, in its evolutionary context, is a vital survival mechanism. It functions as a central component of innate immunity, a "friend" designed to neutralize pathogens, clear necrotic debris, and facilitate tissue repair [3]. This acute response is typically high-grade, localized, and, crucially, self-limiting. However, in the context of modern industrialized environments, this adaptive machinery has maladapted. The immune system is subjected to a relentless barrage of anthropogenic stressors, such as caloric excess, sedentary behavior, environmental toxins, psychosocial stress, and circadian disruption, which trigger a persistent, low-amplitude activation of the immune cascade [4]. This state, often described as "meta-inflammation" or "inflammaging," lacks the resolution phase characteristic of acute immunity, resulting in collateral tissue damage that accumulates over decades [4].

The pervasive nature of this pathology suggests a fundamental discordance between human physiology and the contemporary environment. The "Evolutionary Mismatch Hypothesis" posits that the human genome, selected for scarcity and high physical demand, is ill-equipped for the "obesogenic" and "stressogenic" niche

of the 21st century [6, 7]. Traits that were once advantageous, such as the ability to robustly conserve energy or mount a rapid inflammatory response to injury, now manifest as susceptibility factors for metabolic syndrome and autoimmunity [61].

This report provides an exhaustive analysis of the phenomenon of low-grade inflammation. It dissects the molecular architectures sustaining this state, explores the lifestyle factors driving the "mismatch," evaluates emerging biomarkers capable of quantifying subclinical risk, and synthesizes the clinical evidence supporting anti-inflammatory therapeutic interventions.

Methodology

This narrative review synthesizes current evidence linking chronic low-grade inflammation to the pathogenesis of non-communicable diseases, with a specific focus on molecular mechanisms, emerging biomarkers, and therapeutic interventions. A comprehensive literature search was conducted across major electronic databases, including PubMed/MEDLINE, Scopus, and Google Scholar, prioritizing peer-reviewed articles published within the last two decades to ensure the inclusion of the most recent advancements in the field. The search strategy utilized a combination of terms relevant to the core themes of the review, specifically focusing on low-grade inflammation, the activation of the NLRP3 inflammasome, and the concept of evolutionary mismatch as a driver of modern pathology. Furthermore, specific queries were directed toward advanced diagnostic tools, including general inflammation markers and novel biomarkers such as suPAR and GlycA, as well as therapeutic strategies involving colchicine and the broader field of immunometabolism.

The selection process applied strict inclusion criteria, focusing on original research, meta-analyses, and randomized clinical trials - such as the landmark CANTOS, LoDoCo2, and COLCOT studies - that provided mechanistic insights or clinical validation of the inflammatory hypothesis. Articles were selected based on their relevance to the "common soil" hypothesis, establishing links between lifestyle factors like diet and stress, and molecular pathways such as NF-κB and NLRP3. Data synthesis was qualitative, integrating findings from diverse disciplines including immunology, cardiology, endocrinology, and neurology to construct a unified framework for understanding civilization diseases. A total of 64 key references were selected to support the arguments presented, providing a robust evidentiary basis for the analysis of sterile inflammation, mitochondrial dysfunction, and the gut-brain axis. The review excludes studies focusing solely on acute infectious inflammation or animal models lacking clear translational value to human pathology, ensuring the clinical applicability of the conclusions drawn.

Results

Core Immunological Mechanisms Underlying Chronic Low-Grade Inflammation

The transition from homeostasis to chronic inflammation is not merely a passive consequence of aging but an active, regulated process driven by specific intracellular signaling pathways. Unlike infectious inflammation, which is triggered by pathogen-associated molecular patterns (PAMPs), modern low-grade inflammation is largely "sterile," triggered by damage-associated molecular patterns (DAMPs) and metabolic surplus [9].

At the core of sterile inflammation lies the nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome. This intracellular protein complex acts as a sentinel for metabolic danger [10]. While adaptive immunity relies on specific antigen recognition, the NLRP3 inflammasome responds to a diverse array of cellular stressors prevalent in modern life, including excess glucose, ceramides, uric acid crystals, and environmental toxicants [10, 11].

The activation of the NLRP3 inflammasome operates via a tightly regulated two-signal mechanism, ensuring that potent inflammatory cytokines are not released indiscriminately:

- Priming (Signal 1): The process initiates with the activation of pattern recognition receptors, such as Toll-like receptors (TLRs), by stimuli like lipopolysaccharides (LPS) or free fatty acids. This triggers the nuclear factor-kappa B (NF-κB) signaling pathway, leading to the transcriptional upregulation of NLRP3 and the pro-form of the cytokine interleukin-1 beta (pro-IL-1β) [10].
- Activation (Signal 2): A secondary disturbance, such as mitochondrial dysfunction, potassium efflux, or lysosomal rupture, triggers the assembly of the inflammasome complex. Once assembled, NLRP3 recruits the adaptor protein ASC and pro-caspase-1. The autocatalysis of caspase-1 then cleaves pro-IL-1β and pro-IL-18 into their biologically active forms, which are secreted to propagate the inflammatory signal systemically [11, 13].

This mechanism is distinctively self-perpetuating in chronic disease states. For example, the resultant secretion of IL-1β and IL-18 by macrophages and endothelial cells upregulates adhesion molecules such as VCAM-1 and MCP-1, establishing a feedback loop that drives the progression of atherosclerosis from a fatty streak to a vulnerable plaque [12].

Oxidative stress serves as both an upstream trigger and a downstream consequence of inflammatory activation, creating a vicious cycle of cellular erosion. Modern environmental exposures and metabolic overloads have been linked to increased inflammasome activity via the generation of reactive oxygen species (ROS) [10].

Mitochondria are the primary engines of this dysfunction. In states of metabolic overload, the mitochondrial electron transport chain becomes inefficient, leaking superoxide and other ROS. These ROS can directly activate the NLRP3 inflammasome [10]. The impact of this oxidative stress is systemic; for instance, research indicates that oxidative stress coupled with NLRP3 activation plays a significant role not just in cardiovascular tissues but also in reproductive health and fertility [8]. Furthermore, damaged mitochondria may release mitochondrial DNA (mtDNA) into the cytosol. Because mitochondria are evolutionary descendants of bacteria, their DNA is recognized by the innate immune system as a "foreign" entity (similar to bacterial DNA), triggering a robust inflammatory response even in the absence of infection [13].

Systemic Triggers and Sources of Persistent Inflammatory Signaling

Historically viewed as an inert energy depot, adipose tissue is now recognized as a highly active endocrine organ that secretes bioactive peptides known as adipokines. In obesity, the expansion of adipose tissue leads to hypoxia and macrophage infiltration, shifting the secretory profile toward a pro-inflammatory phenotype [21]. The specific contributions of key adipokines to this inflammatory cascade, contrasting their physiological functions with their pathological roles, are summarized in Table 1.

Table 1. Key Adipokines in Low-Grade Inflammation

Adipokine	Primary Function	Role in Pathology	Clinical Association
Leptin	Satiety regulation; immune modulation	Pro-inflammatory; activates macrophages & T-cells	Levels correlate with BMI & insulin resistance [18, 21]
Adiponectin	Insulin sensitizing; anti-inflammatory	Protective; inhibits NF-κB	Levels are reduced in obesity & metabolic syndrome [22]
Resistin	Induces insulin resistance	Pro-inflammatory; promotes endothelial dysfunction	Linked to low-grade inflammation [18, 24]
Visfatin	Insulin-mimetic; NAD+ regulation	Pro-inflammatory; increases IL-6 & TNF-α	Elevated in obesity, RA, and plaque instability [18, 24]

The dysregulation of these adipokines creates a systemic environment where immune cells are chronically stimulated. For instance, Visfatin (also known as NAMPT) has been shown to bridge the gap between metabolic dysregulation and autoimmunity, with elevated levels found in the synovial fluid of patients with rheumatoid arthritis [64]. Similarly, the leptin/adiponectin ratio has emerged as a more sensitive marker of metabolic risk than BMI alone, reflecting the functional state of the adipose tissue rather than just its mass [23].

The "Western Diet" - characterized by high consumption of saturated fats, ultra-processed foods, and refined sugars, alongside a paucity of fiber - is perhaps the most potent driver of systemic inflammation [4, 25]. Its impact is mediated primarily through the gastrointestinal tract via dysbiosis. This shift in the microbiome degrades the "tight junctions" that seal the gut lining, increasing permeability. This allows the translocation of bacterial endotoxins, specifically lipopolysaccharides (LPS), from the gut lumen into the systemic circulation - a condition known as metabolic endotoxemia [28, 63]. Once in the blood, LPS acts as a potent ligand for TLR4 receptors on immune cells throughout the body, triggering the widespread release of TNF-α, IL-1β, and IL-6 [28].

Environmental and lifestyle drivers

- **Chronic Psychological Stress:** Stress triggers the release of Corticotropin-Releasing Hormone (CRH), which binds to receptors on mucosal mast cells in the gut. This causes degranulation and the release of proteases that degrade tight junctions [27, 28]. Research shows acute stress can significantly increase intestinal permeability in humans, creating a literal physiological breach [27]. Chronic stress sustains this autoimmunity through HPA axis dysregulation and cortisol resistance [30].
- **Sleep Disruption:** Sleep is critical for immunological restoration. Deep sleep suppresses the HPA axis [29]. Sleep deprivation leads to a 24-hour increase in cortisol and inflammation markers like IL-6 and CRP [31]. This creates a feedback loop where inflammation disrupts sleep architecture, and poor sleep exacerbates inflammation [26].
- **Age-related inflammatory drift ("Inflammaging"):** The cumulative effect of these stressors over time leads to an age-related drift toward a pro-inflammatory status, where the immune system remains in a state of low-grade activation, contributing to frailty and disease [9].

Downstream Physiological and Pathological Consequences

The interplay between metabolism and vascular biology provides the clearest example of how low-grade inflammation translates into clinical pathology. The endothelium and the insulin signaling cascade are intimately coupled via a mechanism known as pathway-selective insulin resistance. Under healthy physiological conditions, insulin binding to endothelial receptors activates the protective PI3K/Akt pathway, stimulating the production of nitric oxide (NO) for vasodilation. However, in states of chronic inflammation, pro-inflammatory cytokines and free fatty acids selectively impair this pathway while leaving the MAPK pathway, which stimulates the vasoconstrictor Endothelin-1, intact [17]. This signaling imbalance results in a dangerous hemodynamic phenotype characterized by the loss of vasodilator capacity combined with unopposed vasoconstriction, which mathematical modeling confirms is sufficient to explain the hypertension and vascular stiffness observed in metabolic syndrome [14]. This dysfunction is further exacerbated by glucotoxicity and lipotoxicity; hyperglycemia directly triggers NF-κB activation in the vasculature, while free fatty acids increase reactive oxygen species (ROS) and induce endothelial apoptosis [19]. Consequently, a reciprocal relationship is established where insulin resistance fuels endothelial dysfunction and vice versa, laying the structural groundwork for atherosclerosis [15, 16].

Systemic inflammation extends its pathological reach to the Central Nervous System (CNS) through the Microbiota-Gut-Brain Axis (MGBA). Circulating inflammatory mediators compromise the integrity of the Blood-Brain Barrier (BBB), damaging endothelial cells and pericytes to allow the infiltration of peripheral immune cells and neurotoxic molecules into the brain parenchyma [34, 37]. Additionally, the vagus nerve serves as a conduit for pathology, where afferent fibers sense peripheral cytokine signals and relay them to the brainstem, triggering a central inflammatory response [39]. Biochemically, this inflammation fundamentally alters neurotransmission. Chronic immune activation diverts tryptophan metabolism away from serotonin synthesis and toward the Kynurenine Pathway. This metabolic change has a dual detrimental effect: it depletes serotonin, contributing to mood disorders, and simultaneously generates neurotoxic metabolites like quinolinic acid that cause excitotoxic damage to neurons [24].

At the cellular level, chronic peripheral inflammation acts as a priming signal for microglia, the brain's resident macrophages. These cells shift toward a neurotoxic phenotype, releasing ROS and cytokines that accelerate protein misfolding and aggregation [33]. This mechanism is particularly evident in Parkinson's Disease (PD), where alpha-synuclein aggregation may initiate in the enteric nervous system due to gut dysbiosis and propagate to the brain via the vagus nerve [20, 36]. Similarly, in Alzheimer's Disease, gut-derived metabolites and endotoxins have been shown to cross the BBB and activate NF-κB signaling in the brain, directly promoting amyloid deposition [32, 37]. The temporal scope of this pathology extends even to early development; dysbiosis acquired in early life, such as through C-section delivery, can prime the developing brain for inflammation, increasing the long-term risk for neurodevelopmental disorders like ASD and ADHD [55].

Biomarkers of Low-Grade Inflammation

Diagnosing low-grade inflammation requires tools sensitive enough to distinguish between basal immune activity and subclinical pathology. Currently, high-sensitivity C-reactive protein (hs-CRP) remains the "gold standard" for vascular risk stratification, supported by extensive epidemiological data and clinical guidelines [40, 57]. Synthesized in the liver primarily in response to IL-6 stimulation, hs-CRP serves as a downstream integrator of the inflammatory cascade [12]. Clinical thresholds are well-established: levels <1 mg/L, 1–3 mg/L, and >3 mg/L correspond to low, intermediate, and high cardiovascular risk, respectively [56]. However, the utility of hs-CRP is inherently limited by its lability; as an acute-phase reactant, its levels can spike dramatically due to minor infections or trauma, creating a "noisy" background that may obscure the subtle signal of chronic meta-inflammation [40]. To mitigate this limitation, research has turned to fibrinogen, which provides a mechanistic link between the inflammatory response and the coagulation cascade. Elevated fibrinogen levels not only reflect systemic inflammation but actively promote a pro-thrombotic state by increasing plasma viscosity and platelet aggregation [38]. While direct comparisons often indicate that hs-CRP is a superior independent predictor of mortality, the concurrent assessment of both markers offers additive prognostic value. For instance, in a cohort of over 27,000 women, the combination of high hs-CRP and high fibrinogen was associated with a multivariable-adjusted relative risk of cardiovascular events of 2.4 (95% CI, 1.6 to 3.7) compared to those with low levels of both markers, confirming that multi-marker panels better capture the complexity of atherothrombosis [38, 41].

Limitations of single-protein markers have driven the development of composite biomarkers like GlycA, measured via nuclear magnetic resonance (NMR) spectroscopy. GlycA does not measure a specific protein but rather quantifies the N-acetyl methyl groups of N-acetylglucosamine residues on specific acute-phase proteins (such as α1-acid glycoprotein, haptoglobin, and transferrin) [46]. This provides a stable, composite signal of systemic protein glycosylation, which is altered during chronic inflammation. GlycA offers distinct advantages in the context of metabolic disease. Research indicates that GlycA levels correlate more strongly with indices of adiposity and insulin resistance - specifically the leptin/adiponectin ratio - than with glucose tolerance alone, positioning it as a superior marker for adipose-tissue-driven inflammation [22]. Furthermore, in models of systemic inflammation such as psoriasis, GlycA has demonstrated a stronger association with vascular inflammation (quantified by FDG-PET/CT) and coronary plaque burden than hs-CRP [47]. Its lower intra-individual variability compared to CRP makes it a particularly promising tool for longitudinal monitoring of subclinical risk [22, 46]. Furthermore, in models of systemic inflammation such as psoriasis, GlycA has demonstrated a robust association with vascular inflammation. In a study of patients with psoriasis, GlycA was significantly associated with vascular inflammation quantified by FDG-PET/CT uptake ($\beta = 0.36$, $P < 0.001$), an association that remained significant even after adjusting for hs-CRP. Moreover, GlycA showed lower intra-individual variability (CV = 4.3%) compared to hs-CRP (CV = 29.6%), making it a statistically more reliable tool for longitudinal monitoring of subclinical risk [47].

Perhaps the most robust candidate for surveillance of chronic, age-related inflammation is the soluble urokinase plasminogen activator receptor (suPAR). Unlike CRP, which is a circulating liver protein, suPAR is released directly by activated immune cells (monocytes, neutrophils) and endothelial cells [42]. Its levels are remarkably stable, showing little circadian variation and resisting fluctuations caused by minor acute infections. This stability allows suPAR to function effectively as an "immunological HbA1c," reflecting the aggregate inflammatory burden or "tax" placed on the body over years [42]. The prognostic power of suPAR is extensive. In general population cohorts, elevated suPAR levels are strongly predictive of adverse outcomes. For example, in a study of healthy individuals, higher suPAR levels were associated with increased all-cause mortality (Hazard Ratio [HR] = 1.73 for the highest vs. lowest quartile) and cardiovascular disease (HR = 1.64), independent of traditional risk factors like age, sex, and smoking [43]. Furthermore, meta-analyses confirm its prognostic value in coronary artery disease [45]. In the specific context of cardiac pathology, suPAR has shown significant utility in predicting adverse outcomes in patients with atrial fibrillation. Patients with elevated suPAR levels had a significantly higher risk of all-cause mortality compared to those with low levels, likely by reflecting the degree of atrial structural remodeling driven by chronic inflammation [44]. Thus, suPAR represents a shift from measuring the response to inflammation (like CRP) to measuring the cellular activation state itself.

To synthesize the distinct biological profiles and clinical applications of these diagnostic tools, Table 2 provides a comparative overview. This summary highlights the trade-offs between availability, stability, and specificity that clinicians must navigate when stratifying risk in patients with chronic low-grade inflammation.

Table 2. Comparative Analysis of Inflammatory Biomarkers

Biomarker	Biological Source	Stability	Primary Clinical Indication	Key Advantage
hs-CRP	Liver (IL-6 dependent)	Low (Acute fluctuations)	CVD Risk Stratification (Primary & Secondary Prevention)	Guideline-endorsed; widely available; massive epidemiological data [40, 56]
Fibrinogen	Liver	Moderate	Thrombosis & Inflammation Link	Mechanistically links inflammation to coagulation; additive value to CRP [38]
GlycA	Glycosylated acute-phase proteins	High	Subclinical Atherosclerosis & Metabolic Inflammation	Composite marker; correlates strongly with vascular inflammation imaging & adiposity [22, 47]
suPAR	Immune cells (Neutrophils, Monocytes) & Endothelium	Very High (Stable)	All-cause Mortality & CKD Prognosis	Reflects cellular immune load ("Immunological HbA1c"); high prognostic stability [42, 51]

Therapeutic Pathways and Interventions Targeting Low-Grade Inflammation

We have crossed a threshold in therapeutic strategy: inflammation is no longer viewed merely as a biomarker of disease, but as a modifiable driver of pathology. The important change arrived with the CANTOS trial, which utilized canakinumab to block interleukin-1β. This study provided the definitive "proof of concept" that lowering inflammatory burden (as measured by hs-CRP) reduces cardiovascular risk, regardless of whether lipid levels change [5, 57]. This success paved the way for colchicine, an inexpensive, time-tested drug that inhibits tubulin polymerization and, crucially, prevents the assembly of the NLRP3 inflammasome. Data from the LoDoCo2 and COLCOT trials were transformative, establishing low-dose colchicine as the first FDA-approved anti-inflammatory specifically indicated for reducing atherothrombotic events [50, 51]. However, the failure of the CIRT trial, which relied on the broad-spectrum immunosuppressant methotrexate, taught the medical community a critical lesson: simply dampening the immune system is insufficient. Clinical success depends entirely on specificity - we must intercept the specific NLRP3-IL-1β-IL-6 axis rather than suppressing immunity indiscriminately [57].

Beyond agents designed specifically to fight inflammation, many standard metabolic drugs exert potent "off-target" anti-inflammatory effects that contribute significantly to their clinical success. Statins, the bedrock of cardiovascular prevention, do far more than regulate cholesterol; they actively stabilize the vessel wall by inhibiting adhesion molecule expression and blocking the migration of leukocytes into the endothelium [52]. Similarly, metformin, the standard first-line therapy for type 2 diabetes, acts as a comprehensive brake on cellular aging. By triggering the AMPK pathway, metformin effectively shuts down NF-κB signaling and quiets the NLRP3 inflammasome, thereby mitigating oxidative stress [53]. These molecular mechanisms suggest that metformin could be repurposed to treat "inflammaging" even in non-diabetic populations, potentially working synergistically with exercise to build physiological resilience in older adults [54].

Because modern low-grade inflammation arises largely from a mismatch between human physiology and the surrounding environment, the data consistently point to lifestyle-based measures as the most effective way to counteract this process at its source. In the studies reviewed, physical activity emerged as a particularly strong modulatory factor. Rather than acting only through energy expenditure, regular muscle contraction appeared to influence immune signaling directly. Participants engaging in sustained activity showed an increased release of myokines that dampen inflammatory pathways, lower TLR4 sensitivity, and reduce the immune system’s reactivity to circulating endotoxins. These changes coincided with measurable improvements in endothelial insulin signaling, including better nitric-oxide–dependent vasodilation, suggesting that exercise may interrupt the cycle of metabolic and vascular impairment described earlier [16].

Dietary patterns showed a similar upstream influence. Populations with higher intake of plant fibers and omega-3 fatty acids demonstrated improved gut-barrier integrity and a consistent reduction in circulating inflammatory markers, particularly TNF-α and CRP. Notably, in older cohorts, lower levels of these markers were closely associated with reduced frailty risk, a relationship confirmed across several meta-analyses. These findings reinforce the idea that chronic inflammation acts as an independent predictor of age-related functional decline rather than simply accompanying it [62].

A third line of evidence pointed toward emerging neuromodulatory approaches. Early trials of vagus nerve stimulation (VNS) showed that activating the cholinergic anti-inflammatory pathway can lower both systemic cytokine output and microglial reactivity. Although the sample sizes remain modest, VNS consistently produced anti-inflammatory effects without the pharmacological burden associated with systemic agents, suggesting a potential role as an adjunct intervention [35].

Discussion

Integrating Evidence Across Mechanistic Domains: The "Common Soil" Hypothesis

The evidence synthesized in this review supports a "unifying theory" of chronic disease, dismantling the traditional siloed approach to medicine where organ systems are treated in isolation. The seemingly disparate domains of immunology, metabolism, and microbiology are, in reality, functionally inseparable. This integration rests on the understanding that low-grade inflammation is not merely a secondary symptom of disease, but the primary, shared pathophysiological substrate the "common soil", from which multimorbidity arises [2, 60].

The Convergence of Stressors Modern pathology is defined by the convergence of distinct environmental inputs into a singular immunological output. Whether the upstream insult is metabolic (caloric excess, glucotoxicity) [19], neurological (sleep deprivation, chronic psychosocial stress) [31, 33], or environmental (dietary toxins, pollution), the physiological bottleneck is identical: the activation of the NF-κB signaling pathway and the assembly of the NLRP3 inflammasome [10]. This molecular convergence explains why diverse risk factors,such as a sedentary lifestyle, poor diet, and loneliness, manifest physiologically in remarkably similar ways, ultimately driving the same cascade of oxidative stress and cytokine release [1, 13].

This systemic dysfunction must be viewed through the lens of the Evolutionary Mismatch Hypothesis. The human immune system evolved in an environment of scarcity and high pathogen load, selecting for a robust, rapid inflammatory response to survive injury and infection. In the modern "obesogenic" and "stressogenic" environment, this adaptive machinery has become maladaptive [61]. The continuous, low-level stimulation by "sterile" triggers (DAMPs, nutrient excess) results in a state of non-resolving inflammation or "inflammaging," where the resolution phase of the immune response is never fully achieved, leading to cumulative tissue damage over decades [4, 9].

This integrative model provides a mechanistic explanation for the high rates of comorbidity observed in clinical practice. Diseases are not isolated events but manifestations of systemic failure driven by cross-organ signaling.

- The Metabolic-Psychiatric Link: The connection between Type 2 Diabetes and depression is not purely psychological but biological, mediated by the diversion of tryptophan metabolism toward neurotoxic kynurenines under inflammatory conditions [6, 24].
- The Dermatological-Vascular Link: Patients with psoriasis have a significantly elevated risk of cardiovascular mortality not due to chance, but because the cutaneous inflammation is a visible marker of systemic vascular inflammation, detectable by composite biomarkers like GlycA [47].
- The Gut-Brain-Heart Axis: Dysbiosis acts as a central engine for this crosstalk. A compromised gut barrier ("leaky gut") allows endotoxins to enter circulation, simultaneously promoting atherosclerosis in the heart and neuroinflammation in the brain, effectively linking diet directly to neurodegeneration [32, 63].

In summary, the "common soil" hypothesis posits that categorizing diseases solely by organ (heart, brain, liver) is becoming increasingly obsolete in the face of systemic immunometabolic pathology. Understanding the patient requires measuring and treating the underlying inflammatory burden that connects these systems [2].

Clinical Relevance: Low-Grade Inflammation as a Cross-Disease Pathway

The recognition of low-grade inflammation as a fundamental driver of pathology fundamentally shifts the paradigm of clinical management. It challenges the traditional organ-centric model, suggesting that "cardiovascular risk" is not solely a matter of lipids, nor is "neurodegenerative risk" merely a function of protein aggregates. Instead, these risks are manifestations of a shared immunometabolic dysfunction. This perspective implies that therapeutic interventions targeting inflammation can have pleiotropic benefits across multiple organ systems, offering a more holistic approach to patient care.

In the realm of cardiology, the implications are immediate and practice-changing. The validation of the inflammatory hypothesis through trials like LoDoCo2 and COLCOT has moved anti-inflammatory therapy from theory to guideline-endorsed practice. It validates the use of targeted agents like colchicine alongside standard lipid-lowering statins for high-risk patients. This dual approach addresses both the "fuel" (cholesterol) and the "fire" (inflammation) of atherosclerosis, significantly reducing the risk of recurrent events in patients who remain vulnerable despite optimal lipid control [51].

In metabolic medicine, understanding the inflammatory basis of disease highlights the reciprocal and self-perpetuating nature of insulin resistance and endothelial dysfunction. It suggests that metabolic control cannot be fully achieved without addressing the underlying inflammatory milieu. Therapies that dampen systemic inflammation may improve insulin sensitivity not just by altering signaling pathways, but by restoring endothelial function and improving blood flow to metabolically active tissues. This reinforces the concept that treating the "vessel" is as crucial as treating the "sugar" [15].

Perhaps the most transformative implication lies in neurology. The robust evidence linking gut dysbiosis and systemic inflammation to neurodegeneration suggests that the brain can be treated peripherally. Modifying the microbiome through diet, prebiotics, or fecal transplantation, as well as reducing systemic inflammatory load, emerges as a viable strategy for slowing the progression of diseases like Parkinson's and Alzheimer's. This "outside-in" approach offers a new therapeutic avenue for conditions that have historically proven difficult to treat by targeting the brain alone [32, 40].

Strengths and Limitations of Current Biomarkers: The Signal and the Noise

While high-sensitivity CRP (hs-CRP) remains the clinical standard due to the sheer weight of epidemiological evidence and guideline endorsement [56, 57], biological reality complicates its utility as a standalone marker of chronic meta-inflammation. As synthesized in the liver in response to IL-6, CRP is a downstream acute-phase reactant. Its levels are inherently labile, spiking dramatically in response to minor, biologically irrelevant insults - such as a common cold, minor trauma, or even vigorous exercise [40]. This creates a significant "signal-to-noise" problem: the loud, acute signal of a transient infection can easily drown out the subtle, steady hum of low-grade inflammation that drives atherosclerosis and metabolic dysfunction [46]. Consequently, while effective for population-level risk stratification, hs-CRP can lack the specificity required for precision medicine in individual patients.

In contrast, emerging biomarkers offer a solution to the volatility of CRP. Soluble uPAR (suPAR) stands out for its remarkable stability. Because it is released by activated immune cells (neutrophils, monocytes) and reflects the activation state of the immune system rather than just a cytokine response, it functions as an "immunological HbA1c" [51]. This marker captures the aggregate inflammatory burden placed on the cellular system over time, making it a superior predictor of long-term outcomes like CKD progression and all-cause mortality compared to snapshot measurements of CRP [43, 51]. Similarly, GlycA offers a composite view of the systemic stress response. By quantifying the glycosylation state of multiple acute-phase proteins simultaneously via NMR, it provides a stable signal that correlates strongly with metabolic health and vascular inflammation, often outperforming CRP in conditions characterized by high metabolic flux, such as psoriasis or insulin resistance [22, 47, 54].

Despite the biological superiority of these newer markers, a critical "Screening Controversy" persists. Major regulatory bodies, such as the USPSTF, continue to cite insufficient evidence to recommend routine inflammatory screening in asymptomatic adults [59]. The hesitation isn’t because the tests don’t work - we know they clearly predict disease. The real problem is that we don't yet have a clear roadmap for how to treat the average person based on those resultsWhile guidelines endorse measuring inflammation in "intermediate risk" patients to decide on statin therapy [63], there is currently no universal protocol for treating an elevated suPAR or GlycA level in the absence of traditional risk factors. This highlights a significant gap in translational medicine: we possess high-precision diagnostic tools, but clinical practice lags behind with blunt therapeutic algorithms, restricting these advanced biomarkers to specialized risk assessment rather than primary care.

Therapeutic Implications and Remaining Challenges

The recent history of inflammation-targeted clinical trials underscores a decisive principle: in cardiovascular prevention, therapeutic success depends not on suppressing the immune system broadly but on precisely targeting the molecular pathways that drive residual inflammatory risk. The failure of the CIRT trial, where low-dose methotrexate produced no reduction in cardiovascular events because it did not meaningfully lower IL-6 or CRP, highlighted the limitations of "blunt" immunosuppression [57]. In contrast, the success of CANTOS and the colchicine trials demonstrated that inhibiting the NLRP3 - IL-1β - IL-6 axis can meaningfully reduce vascular events while preserving critical host-defense mechanisms [5, 49]. Together, these findings redefine inflammation not as a generic target but as a network of discrete pathways requiring precise, pathway-specific intervention.

Yet even with validated agents such as colchicine, now FDA-approved for cardiovascular risk reduction, clinical translation remains incomplete. We possess drugs with proven efficacy, but we lack the biomarker-guided frameworks necessary to deploy them rationally in everyday practice. Immunometabolism has no analogue to the LDL-based algorithms that structure lipid management, leaving clinicians without clear criteria for determining who requires anti-inflammatory therapy and on what basis. Key questions remain unanswered, including how to act when biomarkers diverge (e.g., elevated suPAR with normal CRP) or whether genetic predisposition to NLRP3 hyperactivation should influence treatment selection. This absence of standardized, precision-medicine protocols results in a significant implementation gap, where effective therapies remain underutilized not due to lack of efficacy but due to lack of clinical guidance [50, 51].

Even when appropriately targeted, pharmacotherapy alone cannot fully address the upstream drivers of chronic inflammation, which originate not in isolated cytokine pathways but in the broader Evolutionary Mismatch between human physiology and the modern environment. Agents such as canakinumab and colchicine can effectively blunt downstream inflammatory signaling, yet they do not correct foundational disruptions such as impaired gut barrier integrity, sedentary behavior, dysregulated energy intake, or chronic stress exposure [61]. Lifestyle-based strategies such as dietary modulation, regular physical activity, and adequate sleep, remain the only interventions capable of addressing the root causes of the inflammatory burden [4, 62]. However, these behaviors must be enacted within an obesogenic environment that actively opposes them, making adherence the dominant therapeutic barrier. As a result, lifestyle modification represents the etiological cure, whereas pharmacotherapy functions as a necessary, pragmatic bridge for patients unable to counteract the persistent friction imposed by their surroundings.

3.5. Future Directions

The future of chronic disease management lies in the transition from broad, population-based algorithms to the precise science of Personalized Immunometabolism. This change in the focus from treating the "average" patient to understanding the unique biological context of the individual. Central to this approach is deciphering *Genotype x Environment (GxE)* interactions. We are moving toward a clinical reality where we identify individuals with specific genetic predispositions, such as gain-of-function variants in the *NLRP3* gene, that render them disproportionately sensitive to environmental stressors. Identifying these "hyper-responders" early would allow for aggressive, preemptive interventions before the cumulative damage of inflammaging sets in [6].

To achieve this level of resolution, clinical diagnostics must evolve beyond single-protein markers. The integration of multi-omics - combining proteomics (utilizing stable markers like suPAR and GlycA), metabolomics, and deep microbiome sequencing—will enable the construction of high-definition "inflammatory phenotypes." Given the complexity of these datasets, Artificial Intelligence (AI) will play an indispensable role in pattern recognition, distinguishing, for instance, between inflammation driven primarily by gut dysbiosis versus that driven by metabolic glucotoxicity [48, 60]. This granular stratification is essential for moving beyond the vague diagnosis of "chronic inflammation" to precise, actionable pathologic definitions.

Ultimately, these diagnostic advances must translate into **Therapeutic Precision**. Biomarkers should no longer serve merely as passive indicators of risk (prognosis), but as active tools for guiding treatment selection (prediction). Future clinical protocols will likely utilize dynamic biomarker thresholds to dictate the initiation, dosing, and de-escalation of targeted agents like colchicine or IL-1 inhibitors. By reserving potent immunomodulatory therapies for patients with a demonstrable, residual inflammatory burden, we can maximize cardiovascular protection while minimizing unnecessary exposure to immunosuppression, finally bridging the gap between biological potential and clinical reality [5, 58].

Conclusions

Low-grade inflammation is not merely a secondary symptom of disease but the defining physiological signature of the modern age. This review establishes that the "immunological paradox" of the 21st century arises from a fundamental collision between an ancient immune system - evolved for scarcity and acute defense - and an anthropogenic environment characterized by caloric excess, chronic stress, and sedentary behavior. Mechanistically, this evolutionary mismatch drives a persistent, sterile activation of the NLRP3 inflammasome, gut dysbiosis, and oxidative stress loops. These pathways create a "common soil" of pathology that unites diverse conditions, serving as the shared pathophysiological substrate for the dominant non-communicable diseases, from cardiovascular disease and metabolic syndrome to neurodegeneration.

The transition from understanding inflammation as a bystander to recognizing it as a causal driver has profound clinical implications. We have moved beyond the era of non-specific immunosuppression; trials like CANTOS and LoDoCo2 confirm that therapeutic success depends on precisely targeting the NLRP3-IL-1β-IL-6 axis. Consequently, the most effective therapeutic approach is combinatorial: resolving the upstream evolutionary mismatch through lifestyle intervention, augmented by targeted pharmacotherapy (e.g., colchicine) and immunometabolic modulators when necessary.

However, a significant translational gap remains regarding diagnosis. While advanced biomarkers like suPAR and GlycA offer superior stability and prognostic power compared to the traditional hs-CRP, they are not yet integrated into routine clinical decision-making. To bridge this gap, future medicine must embrace a model of Personalized Immunometabolism, utilizing multi-omics to identify high-risk phenotypes and guide precision therapy. Ultimately, the validation of the inflammatory hypothesis marks a turning point in medicine, moving clinical practice from treating isolated symptoms to managing the fundamental "soil" of disease.

Disclosure

Authors' contribution:

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