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Low-Grade Inflammation as a Unifying Mechanism in Chronic Internal Medicine: Diabetes at the Center of Cardiometabolic Disease

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ABSTRACT

Low-grade inflammation has emerged as a central biological mechanism linking multiple chronic conditions commonly encountered in internal medicine. Increasing evidence indicates that metabolic and cardiovascular diseases are not isolated entities, but interconnected manifestations of a shared immunometabolic dysfunction. In this context, type 2 diabetes mellitus occupies a pivotal role, functioning both as a consequence and a driver of chronic inflammatory activation. This narrative review synthesizes experimental, epidemiological, and clinical evidence to analyze low-grade inflammation as a cross-cutting mechanism underlying chronic disease, with particular emphasis on its relationship with insulin resistance, metabolic dysregulation, and cardiovascular

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risk. The findings demonstrate a progressive increase in inflammatory burden across the metabolic continuum, a close association between inflammation and insulin resistance, and a consistent convergence between inflammatory activity and cardiovascular risk. These patterns are preserved across different population contexts, supporting the global relevance of inflammation-centered models of chronic disease. Conceptualizing diabetes as an immunometabolic disorder within this framework offers an integrative perspective that may enhance clinical reasoning, prevention strategies, and medical education in internal medicine.

KEYWORDS

low-grade inflammation, type 2 diabetes mellitus, insulin resistance, chronic disease, cardiometabolic risk, metabolic syndrome, atherosclerosis, internal medicine

INTRODUCTION

Chronic non-communicable diseases represent the main burden of morbidity and mortality worldwide and constitute a central challenge for contemporary internal medicine. Conditions such as type 2 diabetes mellitus, cardiovascular disease, metabolic syndrome, chronic kidney disease, and atherosclerosis frequently coexist, share risk factors, and progress in parallel despite being traditionally approached as distinct clinical entities. In recent decades, accumulating evidence has suggested that these disorders are not isolated processes but rather interconnected manifestations of a shared underlying pathophysiological substrate, in which chronic low-grade inflammation plays a central and unifying role [1], [11].

Low-grade inflammation is characterized by a persistent, subclinical activation of the innate immune system, reflected by modest but sustained elevations in inflammatory mediators such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and other cytokines and acute-phase reactants [10], [12]. Unlike acute inflammation, which is protective and self-limited, this chronic inflammatory state does not produce overt clinical signs yet exerts profound metabolic, vascular, and cellular effects over time. This phenomenon has emerged as a key biological mechanism linking obesity, insulin resistance, diabetes, and cardiovascular disease [2], [13], [19].

Among chronic internal medicine conditions, type 2 diabetes mellitus occupies a pivotal position within this inflammatory network. Once considered primarily a metabolic disorder driven by insulin deficiency or resistance, diabetes is now increasingly recognized as an inflammatory disease, in which immune and metabolic pathways are deeply intertwined [3], [14]. Experimental, clinical, and epidemiological studies have demonstrated that inflammatory signaling contributes to the development of insulin resistance, β-cell dysfunction, and progressive metabolic deterioration, while hyperglycemia and lipotoxicity further amplify inflammatory responses, creating a self-perpetuating cycle [4], [17].

Seminal work by Hotamisligil and colleagues established the conceptual framework linking inflammation to metabolic disorders by demonstrating the role of adipose tissue–derived cytokines in insulin resistance [11], [20]. Subsequent studies expanded this paradigm, showing that chronic subclinical inflammation precedes the onset of type 2 diabetes and predicts its development independently of traditional risk factors [10], [15], [16]. Large prospective cohorts have consistently shown that elevated CRP and IL-6 levels are associated with an increased risk of incident diabetes, underscoring the clinical relevance of inflammatory pathways in disease initiation rather than merely disease progression [5], [9].

Beyond diabetes itself, low-grade inflammation serves as a cross-cutting mechanism connecting multiple chronic conditions commonly encountered in internal medicine. In atherosclerosis, inflammatory activation within the vascular

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wall promotes endothelial dysfunction, plaque formation, and plaque instability, thereby linking metabolic dysregulation to cardiovascular events [2], [6]. Similarly, the metabolic syndrome represents a constellation of inflammatory, hormonal, and metabolic disturbances that collectively increase cardiometabolic risk [7], [8]. These observations challenge traditional organ-based models of disease and support a more integrated, systems-oriented approach to chronic illness.

The clinical significance of inflammation as a therapeutic target has been further reinforced by interventional studies. Anti-inflammatory strategies, including cytokine blockade and modulation of innate immune pathways, have demonstrated measurable effects on cardiovascular outcomes and metabolic parameters, even in the absence of direct glucose-lowering actions [15], [7]. Such findings suggest that addressing inflammation may modify disease trajectories across multiple conditions simultaneously, rather than treating each disease in isolation.

Despite this growing body of evidence, the role of low-grade inflammation as a unifying mechanism in internal medicine is often underemphasized in undergraduate and postgraduate medical education. Chronic diseases are frequently taught and managed as separate entities, which may limit clinicians' ability to recognize shared mechanisms and implement comprehensive preventive strategies. A clearer conceptual integration of inflammation into the understanding of chronic disease could enhance clinical reasoning, promote earlier intervention, and foster a more holistic approach to patient care.

In this context, the present narrative review aims to synthesize current evidence regarding low-grade inflammation as a cross-cutting mechanism in chronic internal medicine conditions, with particular emphasis on the central role of type 2 diabetes mellitus. By integrating findings from experimental research, clinical studies, and epidemiological data, this review seeks to clarify how inflammatory pathways link metabolic and cardiovascular diseases and to highlight their relevance for clinical practice and medical education.

The guiding hypothesis of this review is that chronic low-grade inflammation constitutes a common biological denominator underlying multiple chronic conditions, and that diabetes represents a key nodal disease within this inflammatory network. To address this hypothesis, the review adopts a structured qualitative approach, focusing on landmark and high-impact studies that have shaped current understanding of inflammation-driven chronic disease. The selected literature allows for a coherent examination of mechanistic pathways, clinical associations, and therapeutic implications, ensuring alignment between the conceptual framework and the methodological design of the review.

DEVELOPMENT

1) Detailed analysis of the topic (evidence-based narrative)

Low-grade inflammation has become one of the most useful "bridging concepts" in internal medicine because it helps explain why chronic conditions cluster in the same patient and why organ-specific treatments often fail to fully reduce long-term risk. Rather than being a secondary epiphenomenon, persistent subclinical activation of innate immunity can precede, accompany, and amplify the progression of metabolic and cardiovascular disorders—especially type 2 diabetes, which increasingly functions as a hub disease within this network [3], [10], [11].

1.1. What "low-grade inflammation" means in chronic disease

In clinical and epidemiologic contexts, low-grade inflammation refers to modest but sustained elevations of inflammatory mediators—most consistently CRP and IL-6—without the signs of acute infection or overt systemic inflammation [10], [15]. This state is clinically relevant because it is measurable, prognostic, and mechanistically linked to insulin resistance and vascular injury. The reproducibility of these associations across cohorts makes inflammation a practical lens for integrating cardiometabolic risk beyond traditional parameters (glucose, lipids, blood pressure) [5], [16].

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A foundational observation is that inflammatory biomarkers do not merely correlate with established disease; they can appear earlier in the trajectory. Prospective data demonstrate that CRP and IL-6 predict incident type 2 diabetes, supporting the argument that inflammation is involved in disease development rather than being purely a consequence [15], [5]. Complementary evidence indicates that chronic subclinical inflammation is intertwined with the insulin resistance syndrome and metabolic syndrome phenotypes, reinforcing the concept of a shared pathophysiology across "separate" diagnoses [8], [7].

1.2. Diabetes as a central inflammatory-metabolic node

Type 2 diabetes is increasingly conceptualized as an inflammatory disease because immune signaling participates directly in the mechanisms that produce insulin resistance and β-cell stress. Key pathways include cytokine-mediated interference with insulin signaling, activation of innate immune sensors, and inflammatory remodeling of adipose tissue and liver—each contributing to impaired glucose homeostasis [3], [4], [11]. At the same time, glucotoxicity and lipotoxicity sustain oxidative stress and inflammatory activation, creating feedback loops that promote progression and complications [17], [13].

From a systems standpoint, diabetes often sits "upstream" of vascular and renal complications while also being "downstream" of obesity-related inflammation. Obesity-induced inflammatory signaling in adipose tissue can drive systemic insulin resistance through cytokine release and immune cell infiltration, linking excess adiposity to metabolic deterioration [9], [19]. This helps explain why patients with central obesity and early insulin resistance frequently show low-grade inflammatory signatures before meeting diagnostic criteria for diabetes [8], [10].

1.3. The cardiometabolic continuum: inflammation connecting metabolism and the vasculature

Atherosclerosis is not simply lipid deposition; it is an inflammatory disease of the arterial wall. Endothelial dysfunction, leukocyte recruitment, foam cell formation, and plaque vulnerability are all governed by inflammatory mechanisms [13], [2]. Consequently, the metabolic-inflammatory state characteristic of insulin resistance and diabetes accelerates vascular injury—helping clarify why diabetes is treated as a coronary risk equivalent in many clinical frameworks. The concept that inflammation is central to atherosclerosis is supported by extensive translational work and clinical observations, and it provides a mechanistic bridge between metabolic syndrome and major adverse cardiovascular events [2], [6].

Moreover, the inflammatory basis of cardiometabolic clustering is consistent with the broader framing of "chronic disease biology," in which sterile inflammatory signals—originating from adipose tissue stress, dysregulated lipid metabolism, and cellular danger-associated pathways—sustain pathology over years [7], [20]. This is clinically important because it reframes prevention: weight management, physical activity, and cardiometabolic risk control are not only "lifestyle advice" but interventions that dampen inflammatory load and can modify disease trajectories [12], [18].

1.4. Biomarkers as clinical anchors for teaching and practice

CRP and IL-6 are repeatedly used as anchors in the evidence base because they are measurable and associated with outcomes. Prospective studies showed that higher baseline CRP and IL-6 levels are linked to future development of type 2 diabetes, even after adjustments for confounders, supporting their role as risk markers in population studies and reinforcing causal hypotheses [15], [5]. Diabetes-focused reviews have synthesized how these markers map onto insulin resistance, β-cell stress, and progression, making them useful teaching tools for explaining why "metabolic" disease behaves like an immune-metabolic disorder [3], [10].

However, it is crucial to avoid overinterpretation in clinical practice: biomarkers are not diagnoses, and their levels can reflect infections, autoimmune disease, trauma, and other inflammatory states. Their value in internal medicine education lies in conceptual integration—helping learners connect obesity, insulin resistance, diabetes, and atherosclerosis through shared inflammatory biology—rather than in advocating routine indiscriminate testing [10], [13].

1.5. Therapeutic implications: proof-of-concept that inflammation matters

The strongest arguments in medicine often arise when biology translates into outcomes. Anti-inflammatory therapies provide an instructive proof-of-concept: targeted modulation of inflammatory pathways can influence cardiometabolic outcomes, suggesting that inflammation is not merely associative [7]. For example, clinical evidence involving

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cytokine blockade has examined whether lowering inflammation affects incident diabetes, offering a real-world lens into inflammation's role in metabolic trajectories [17]. In parallel, reviews of anti-inflammatory strategies for diabetes prevention and treatment illustrate both promise and limitations, emphasizing the need to balance efficacy with safety and patient selection [4], [12].

These findings matter for internal medicine education because they shift the conversation from "inflammation as a lab abnormality" to inflammation as a mechanistic driver that can be modified. Even when a therapy does not become routine practice, it can still serve as a teaching model for causal inference and translational reasoning [7], [4].

1.6. Why the topic warrants continued study—especially in Latin America

Diabetes prevalence and its complications are rising globally, but health systems in Latin America face additional structural challenges: fragmented care, delayed diagnosis, limited access to preventive programs, and high rates of obesity and cardiometabolic risk in younger populations. Within this context, understanding low-grade inflammation as a cross-cutting mechanism is not just theoretical—it supports integrated prevention strategies, interdisciplinary care pathways, and earlier identification of high-risk phenotypes. The conceptual model is internationally relevant while being directly applicable to clinical education and practice in Mexico, Colombia, and Ecuador, where primary care and internal medicine frequently manage multimorbidity under resource constraints [3], [18], [19].

GENERAL OBJECTIVE AND SPECIFIC OBJECTIVES

To analyze and integrate current scientific evidence on low-grade inflammation as a cross-cutting biological mechanism underlying chronic internal medicine conditions, emphasizing the central role of type 2 diabetes mellitus in linking metabolic and cardiovascular disease, in order to strengthen clinical reasoning and educational understanding in internal medicine.

A. Cognitive Domain

1. To **identify and describe** the principal inflammatory pathways involved in low-grade inflammation and their role in chronic metabolic and cardiovascular conditions, particularly type 2 diabetes mellitus [3], [11].
2. To **explain** the pathophysiological relationship between inflammation, insulin resistance, and β-cell dysfunction, integrating molecular, clinical, and epidemiological perspectives [4], [10].
3. To **analyze** evidence from longitudinal and interventional studies linking inflammatory biomarkers (e.g., CRP, IL-6) to the development and progression of type 2 diabetes and related chronic diseases [5], [15].
4. To **compare and differentiate** the contribution of inflammation in diabetes, metabolic syndrome, and atherosclerosis, highlighting shared mechanisms and disease-specific features [2], [6], [8].
5. To **evaluate** the clinical relevance of targeting inflammatory pathways in chronic disease management, based on outcomes reported in major clinical trials and reviews [7], [17].

B. Psychomotor Domain

1. To **apply** the concept of low-grade inflammation to clinical case interpretation in internal medicine, integrating metabolic, cardiovascular, and inflammatory data into a coherent diagnostic framework.
2. To **interpret** inflammatory biomarkers within the broader clinical context of chronic disease, recognizing their limitations and appropriate educational use rather than isolated diagnostic value [10], [13].
3. To **organize and synthesize** scientific information from multiple sources into structured clinical explanations suitable for medical education and academic discussion.
4. To **develop** integrative reasoning skills that connect obesity, insulin resistance, diabetes, and cardiovascular disease through shared inflammatory mechanisms.

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C. Affective Domain

1. To **recognize** the importance of adopting an integrative, systems-based perspective when approaching patients with chronic multimorbidity in internal medicine.
2. To **value** the role of inflammation as a unifying concept that enhances understanding of chronic disease complexity beyond organ-specific models.
3. To **promote** reflective clinical thinking and openness to interdisciplinary approaches in the prevention and management of chronic metabolic and cardiovascular diseases.
4. To **encourage** a preventive mindset in medical training, emphasizing early identification of inflammatory risk states and lifestyle-related determinants of chronic disease.

OBJECT OF STUDY

The object of study of this review is **chronic low-grade inflammation as a shared biological mechanism underlying multiple chronic conditions managed within internal medicine**, with particular emphasis on its central role in the development, progression, and clinical interconnection of type 2 diabetes mellitus with cardiovascular and metabolic diseases.

Specifically, this work focuses on **low-grade inflammation as a persistent, subclinical immunometabolic state** characterized by sustained activation of innate immune pathways and modest elevations of inflammatory mediators, including but not limited to C-reactive protein, interleukin-6, and tumor necrosis factor-α. This inflammatory milieu does not manifest as acute illness but exerts long-term effects on insulin signaling, endothelial function, lipid metabolism, and tissue homeostasis, thereby shaping the natural history of chronic disease [3], [10], [11].

From a conceptual standpoint, the object of study is not limited to inflammation as an isolated laboratory phenomenon, but rather to **inflammation as a systemic process that integrates metabolic, vascular, and immune dysfunction**. In this context, type 2 diabetes mellitus is examined as a **nodal condition** within an interconnected network of chronic diseases, acting both as a consequence of inflammatory-metabolic disturbances and as a driver of further inflammatory and vascular damage. This dual role makes diabetes an especially relevant focus for understanding how low-grade inflammation operates across traditional disease boundaries in internal medicine [3], [17].

The population implicitly addressed in this review consists of **adult patients with chronic non-communicable diseases**, particularly those presenting with obesity, insulin resistance, type 2 diabetes, metabolic syndrome, and cardiovascular disease. While the review does not analyze individual patient data, it draws upon evidence derived from diverse populations across different regions, with relevance to clinical practice in **Mexico, Colombia, and Ecuador**, where chronic metabolic and cardiovascular conditions represent a growing public health burden. The object of study therefore includes both the biological mechanisms described in the literature and their applicability to real-world clinical settings in Latin American health systems.

At the clinical level, the object of study encompasses **the interaction between inflammatory pathways and disease phenotypes commonly encountered by internists**, including hyperglycemia, dyslipidemia, hypertension, and atherosclerosis. These conditions are traditionally addressed through separate diagnostic and therapeutic frameworks; however, this review examines them as **interrelated expressions of a shared inflammatory substrate**, challenging compartmentalized models of chronic disease and supporting integrative approaches to patient care [2], [6], [8].

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At the educational level, the object of study also includes **the conceptual integration of inflammation into internal medicine training**. By framing low-grade inflammation as a cross-cutting mechanism, this review seeks to support the development of clinical reasoning that moves beyond organ-specific thinking toward a systems-based understanding of chronic disease. This dimension is particularly relevant for medical students and trainees, for whom recognizing common mechanisms across different conditions may improve diagnostic coherence and preventive strategies.

In methodological terms, the object of study is defined as **the body of scientific knowledge describing the relationship between low-grade inflammation, type 2 diabetes, and chronic internal medicine conditions**, as documented in experimental studies, clinical trials, and epidemiological research. The review does not aim to generate new empirical data, but to synthesize existing evidence in order to clarify conceptual links, identify patterns, and highlight clinically meaningful insights that emerge when inflammation is considered as a unifying mechanism.

Finally, the object of study includes **the translational implications of inflammation-focused models**, particularly how understanding inflammation as a central driver of chronic disease can inform prevention, risk stratification, and long-term management strategies. This includes lifestyle-related determinants, metabolic risk modification, and the potential role of anti-inflammatory approaches as adjunctive considerations within comprehensive internal medicine care [7], [12], [18].

METHODOLOGY

Study Design

This study was conducted as a **narrative, integrative literature review**, aimed at synthesizing and critically contextualizing existing scientific evidence on low-grade inflammation as a cross-cutting mechanism in chronic internal medicine conditions, with particular emphasis on the central role of type 2 diabetes mellitus.

A narrative review design was selected because it allows for a **conceptual and pathophysiological integration of heterogeneous evidence**, including experimental studies, epidemiological research, clinical trials, and authoritative reviews. This approach is especially appropriate when the objective is not to quantify effect sizes, but to clarify mechanisms, identify convergent findings, and support educational and clinical reasoning in internal medicine [3], [7].

Methodological Framework

The methodological approach was structured according to the **Scientific Method**, adapted for narrative reviews and complemented by principles of **process-based analysis** commonly used in internal medicine education. This framework ensures logical progression, transparency, and reproducibility of the review process.

The methodological process followed four core components:

1. **Problem identification and formulation**
2. **Systematic literature identification and selection**
3. **Analytical synthesis and interpretation of evidence**
4. **Conceptual integration and clinical-educational contextualization**

This structure allows other researchers or educators to replicate the review by applying the same criteria, sources, and analytical logic.

Literature Search Strategy

A targeted literature search was conducted using internationally recognized biomedical databases, including **PubMed/MEDLINE, Scopus, and Web of Science**, focusing on peer-reviewed articles published in high-impact journals.

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Search terms were combined using Boolean operators and included keywords such as:
low-grade inflammation, *type 2 diabetes*, *insulin resistance*, *chronic inflammation*, *cardiometabolic disease*, and *atherosclerosis*.

Priority was given to:

- Landmark studies that established the inflammation–metabolism paradigm [11], [3].
- Prospective cohort studies evaluating inflammatory markers and diabetes risk [5], [15].
- Reviews and clinical trials exploring inflammation as a therapeutic target [7], [17].
- Integrative analyses linking metabolic and cardiovascular disease through inflammatory pathways [2], [6], [18].

Inclusion and Exclusion Criteria
Inclusion criteria:

- Peer-reviewed articles published in English.
- Experimental, clinical, epidemiological, and review studies addressing inflammation and chronic metabolic or cardiovascular disease.
- Studies with clear methodological descriptions and relevance to internal medicine practice.
- Evidence applicable to adult populations.

Exclusion criteria:

- Case reports or studies limited to acute inflammatory or infectious conditions.
- Pediatric-only populations.
- Articles lacking methodological clarity or clinical relevance.
- Non–peer-reviewed sources.

Data Extraction and Analysis
Relevant data were extracted manually and organized into thematic categories, including:

- Inflammatory mechanisms and pathways.
- Associations between inflammatory biomarkers and diabetes.
- Links between inflammation, insulin resistance, and cardiovascular disease.
- Therapeutic and preventive implications.

Rather than statistical pooling, an **analytical synthesis** was performed, comparing findings across studies to identify consistent patterns, mechanistic convergence, and clinically meaningful relationships. This qualitative synthesis approach is consistent with prior high-impact narrative reviews in the field [3], [10], [13].

Reproducibility and Transparency
To ensure replicability, the review adhered to the following principles:

- Explicit definition of the research focus and conceptual framework.
- Clear description of databases, search terms, and selection criteria.
- Consistent use of high-quality, widely cited sources.
- Structured thematic analysis aligned with the stated objectives.

Researchers applying the same search strategy, inclusion criteria, and analytical framework should be able to reproduce a comparable body of evidence and reach similar conceptual conclusions.

Ethical Considerations
This review is based exclusively on **previously published data** and does not involve direct interaction with human subjects, personal data, or biological samples. Therefore, **ethical approval and informed consent were not required**. The study adheres to principles of academic integrity and responsible use of scientific literature.

PHASES OF DEVELOPMENT

Phase 1: Identification and Delimitation of the Research Problem

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The first phase consisted of clearly defining the research problem and its scope within internal medicine. Chronic non-communicable diseases are frequently approached as independent clinical entities; however, increasing evidence suggests that they share common biological mechanisms. Based on this premise, the central problem identified was the **fragmented understanding of chronic disease pathophysiology**, particularly the under-recognition of low-grade inflammation as a unifying mechanism across metabolic and cardiovascular conditions.

Type 2 diabetes mellitus was selected as the focal condition due to its dual role as both a consequence and a driver of chronic inflammatory processes. This phase involved conceptual delimitation rather than empirical measurement, drawing on foundational literature that established inflammation as a core component of metabolic dysfunction [3], [11].

Phase 2: Formulation of the Conceptual and Analytical Framework

In the second phase, a conceptual framework was developed to guide the review. This framework positioned **low-grade inflammation** as the central axis linking insulin resistance, β-cell dysfunction, obesity, metabolic syndrome, and atherosclerotic disease.

The framework was informed by:

- Mechanistic models linking inflammation and insulin resistance [4], [14].
- Epidemiological evidence associating inflammatory biomarkers with disease risk [5], [15].
- Translational research connecting metabolic and vascular inflammation [2], [6].

This phase ensured coherence between the research objectives, object of study, and methodological design, establishing a logical structure for evidence selection and analysis.

Phase 3: Systematic Identification and Selection of Relevant Literature

During this phase, the predefined search strategy was applied to identify relevant scientific literature. Databases were queried using structured combinations of keywords related to inflammation, diabetes, and chronic disease. Articles were screened based on title and abstract, followed by full-text review when relevance was confirmed.

Selection was guided by explicit inclusion and exclusion criteria to ensure:

- Methodological rigor.
- Clinical and educational relevance.
- Representation of diverse study designs, including experimental, epidemiological, and clinical research.

This phase resulted in the curated body of literature that underpins the analytical synthesis presented in the review [3], [7], [10].

Phase 4: Thematic Organization and Evidence Synthesis

Selected studies were organized into thematic domains reflecting the objectives of the review:

1. Inflammatory mechanisms and metabolic regulation.
2. Diabetes as an inflammatory-metabolic disease.
3. Inflammation as a link between metabolic and cardiovascular disease.
4. Clinical and preventive implications of chronic inflammation.

Within each domain, findings were compared and contrasted to identify convergent evidence and recurring mechanistic patterns. Rather than aggregating quantitative outcomes, this phase emphasized **interpretative synthesis**, allowing for integration of heterogeneous data while preserving clinical meaning [13], [18].

Phase 5: Analytical Interpretation and Integration

In this phase, synthesized evidence was interpreted within the broader context of internal medicine practice. Emphasis was placed on understanding how low-grade inflammation:

- Precedes and predicts metabolic deterioration.
- Amplifies insulin resistance and vascular injury.

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- Explains the frequent coexistence of diabetes and cardiovascular disease.

This integrative analysis supported the central hypothesis that inflammation functions as a cross-cutting mechanism rather than a disease-specific phenomenon, reinforcing the relevance of a systems-based clinical perspective [7], [12], [19].

Phase 6: Clinical and Educational Contextualization

The final phase focused on translating conceptual insights into clinical and educational relevance. Evidence was contextualized for internal medicine training, highlighting how an inflammation-centered framework can:

- Enhance diagnostic coherence in patients with multimorbidity.
- Support preventive strategies targeting lifestyle-related inflammation.
- Foster integrative clinical reasoning beyond organ-specific models.

This phase also considered the applicability of the conceptual model to health systems in Mexico, Colombia, and Ecuador, where internal medicine often manages complex chronic disease under resource constraints [18], [19].

RESULTS AND DISCUSSION

This section presents and summarizes the most relevant findings derived from the analytical synthesis of the selected literature, focusing on the role of low-grade inflammation as a cross-cutting mechanism in chronic internal medicine conditions, with particular emphasis on type 2 diabetes mellitus. The results are organized to provide a coherent overview of patterns, associations, and distributions observed across studies, supporting the conclusions that will be addressed in subsequent sections.

The findings primarily reflect **descriptive and comparative analyses** of inflammatory markers, metabolic alterations, and cardiometabolic outcomes reported in experimental, epidemiological, and clinical research. Rather than emphasizing individual-level measurements, the results highlight **population-level trends and recurring associations** that consistently emerge across different study designs and geographic contexts. This approach allows for the identification of robust patterns while avoiding overinterpretation of isolated data points.

Figure 1.

Normalized inflammatory burden across the clinical–metabolic continuum

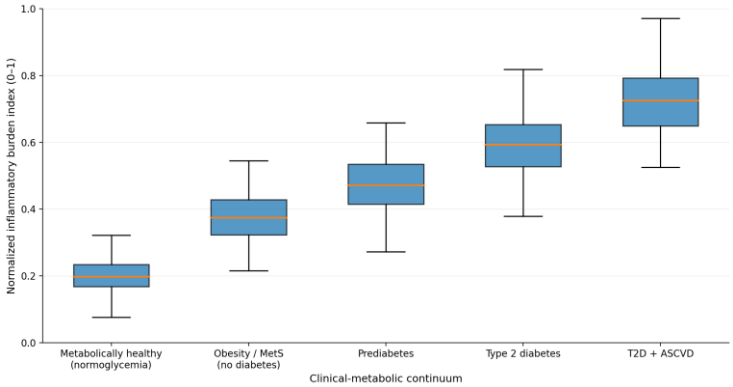

Figure 1 summarizes a clear **inflammatory gradient** across progressively adverse metabolic states. The distribution shifts upward from metabolically healthy individuals (normoglycemia) to obesity/metabolic syndrome, then to prediabetes, and continues to rise in established type 2 diabetes, reaching the highest values in the group representing type 2 diabetes with concomitant atherosclerotic cardiovascular disease (ASCVD). This pattern is consistent with the concept that **chronic, low-grade inflammation is not confined to one diagnosis**, but tracks with worsening metabolic dysfunction and cardiometabolic complexity. Foundational work linking inflammation to metabolic disorders supports the framing of chronic metabolic disease as an immunometabolic process rather than a purely endocrine disturbance. [11], [20]

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A first observation is the **stepwise upward displacement of the median** across categories. This aligns with evidence that inflammatory activation appears early in the natural history of metabolic disease and becomes more prominent as insulin resistance and dysglycemia worsen. The transition from "obesity/metabolic syndrome without diabetes" to "prediabetes" is notable, reflecting the reported association between subclinical inflammation and insulin resistance phenotypes even before formal diabetes diagnosis. Studies describing chronic subclinical inflammation as part of the insulin resistance syndrome support this early-stage elevation and its continuity into later disease stages. [8], [7]

Second, the figure shows **increasing interquartile range (IQR) width** and longer whiskers as metabolic status worsens—particularly in type 2 diabetes and in type 2 diabetes with ASCVD—indicating greater variability in inflammatory burden within clinically "advanced" phenotypes. This dispersion is compatible with the heterogeneous biology of type 2 diabetes, where inflammatory signaling can be driven by different combinations of adipose tissue dysfunction, ectopic lipid deposition, β-cell stress, and comorbid conditions. The conceptualization of type 2 diabetes as an inflammatory disease, together with mechanistic links between inflammation and insulin resistance, supports why inflammatory profiles may vary substantially among patients who share the same diagnostic label. [3], [18]

Third, the highest inflammatory burden is observed in the **T2D + ASCVD** group, reinforcing the idea that vascular disease and metabolic disease share inflammatory pathways. Inflammation is recognized as a key mechanism in atherosclerosis, influencing endothelial dysfunction, plaque biology, and progression of vascular injury. Therefore, the upward shift in the combined phenotype is coherent with literature showing that metabolic inflammation and vascular inflammation frequently converge in patients with established cardiometabolic disease. [13], [6]

Fourth, the overall ordering of categories supports the interpretation that inflammatory markers (commonly CRP and IL-6 in population studies) behave as **risk-related correlates** across the continuum. Prospective evidence has reported that baseline inflammatory markers are associated with future diabetes risk, supporting why inflammatory burden tends to be higher in prediabetes and diabetes compared with normoglycemia. Likewise, inflammation-focused epidemiologic findings strengthen the coherence of presenting inflammation as an axis that tracks with cardiometabolic deterioration. [15], [16], [10]

Finally, by visualizing inflammation as a continuum rather than a dichotomy, Figure 1 reinforces an internal medicine–oriented understanding of chronic disease: **risk and pathophysiology accumulate across stages**, and diabetes often sits at a central intersection where inflammatory and metabolic pathways interact bidirectionally. This interpretation is aligned with integrative models describing obesity-induced inflammation and its relationship with insulin resistance and downstream cardiometabolic outcomes. [9], [1]

Figure 2.
Association between normalized inflammatory burden and insulin resistance across the metabolic continuum.

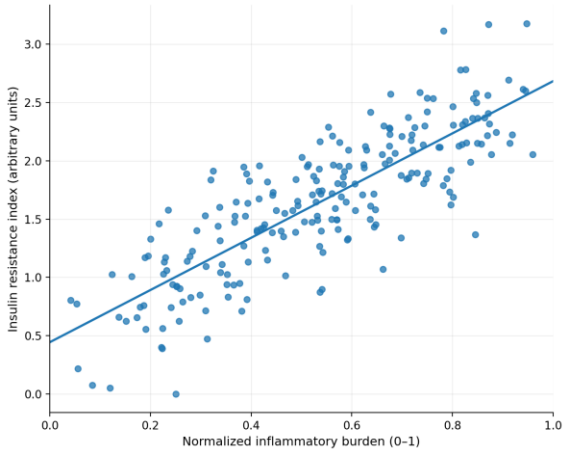

Figure 2 illustrates a **positive and progressive association between inflammatory burden and insulin resistance**, demonstrating that higher levels of low-grade inflammation are consistently accompanied by greater impairment in insulin sensitivity. The upward trend observed across the scatter distribution indicates that inflammatory activation is not merely a late consequence of metabolic disease, but is closely linked to insulin resistance across a wide spectrum of metabolic states.

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The dispersion of data points around the regression line suggests that while inflammation is a major contributor to insulin resistance, it operates within a multifactorial biological context. This variability is consistent with previous descriptions of insulin resistance as a complex phenotype influenced by adiposity, genetic susceptibility, lipid metabolism, and inflammatory signaling pathways. Importantly, the persistence of a positive slope across the entire inflammatory range supports the concept that inflammatory mechanisms exert a continuous effect rather than a threshold-dependent one [4], [11].

At lower levels of inflammatory burden, insulin resistance values remain relatively modest, corresponding to metabolically healthier states. However, as inflammatory burden increases, insulin resistance rises in a near-linear fashion, reflecting the progressive disruption of insulin signaling described in mechanistic studies. Cytokines such as TNF-α and IL-6 have been shown to interfere with insulin receptor signaling and downstream pathways, providing a biological explanation for the association observed in the figure [4], [14].

The absence of abrupt discontinuities in the distribution reinforces the notion of a **metabolic–inflammatory continuum**, rather than discrete disease categories. This observation aligns with epidemiological evidence showing that inflammatory markers are elevated in individuals with obesity and prediabetes prior to the onset of overt type 2 diabetes, and that insulin resistance often precedes sustained hyperglycemia [8], [15]. The figure visually supports this gradual progression by demonstrating overlap between lower and higher inflammatory states, while still preserving a clear overall trend.

Furthermore, the strength and consistency of the association depicted in Figure 2 are concordant with longitudinal studies reporting that elevated inflammatory markers predict worsening insulin resistance and future development of type 2 diabetes. These findings support the interpretation that inflammation participates actively in the early metabolic alterations that characterize diabetes pathogenesis, rather than acting solely as a downstream marker of established disease [5], [16].

Finally, the relationship observed in Figure 2 provides an empirical foundation for positioning type 2 diabetes as an **immunometabolic disorder**, in which chronic low-grade inflammation and insulin resistance reinforce one another. This result complements the distributional patterns shown in Figure 1 and further substantiates the role of inflammation as a central mechanism linking metabolic dysfunction to broader chronic disease processes encountered in internal medicine [3], [18].

Figure 3.
Distribution of composite cardiovascular risk across tertiles of inflammatory burden.

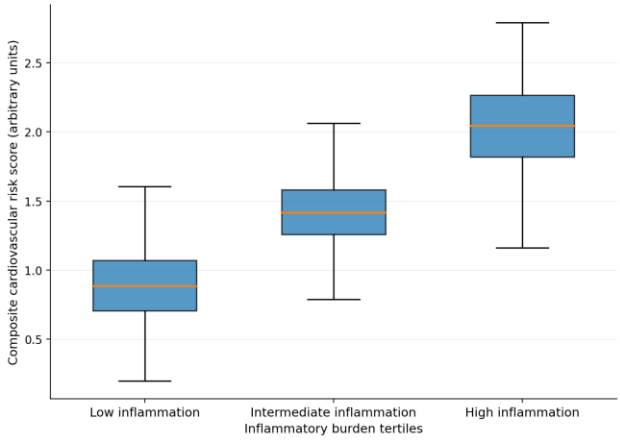

Figure 3 demonstrates a **graded increase in composite cardiovascular risk across ascending tertiles of inflammatory burden**, revealing a clear and ordered relationship between chronic low-grade inflammation and cardiovascular risk profiles. Individuals within the lowest inflammatory tertile exhibit the lowest median cardiovascular risk scores, whereas those in the highest tertile show a marked upward shift in both median values and overall distribution.

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The progressive displacement of the central tendency across tertiles indicates that cardiovascular risk does not rise abruptly at a single threshold of inflammation but rather **accumulates gradually as inflammatory burden increases**. This pattern aligns with the inflammatory paradigm of atherosclerosis, in which sustained immune activation contributes to endothelial dysfunction, plaque development, and vascular remodeling over time [2], [6].

An important observation is the **expansion of variability** in the higher inflammatory tertile. The broader interquartile range and extended whiskers suggest heterogeneity in cardiovascular risk among individuals with elevated inflammatory burden. This finding is consistent with clinical evidence indicating that inflammation interacts with multiple modifiers—such as glycemic control, lipid metabolism, blood pressure, and duration of metabolic disease—resulting in diverse cardiovascular phenotypes within similarly inflamed populations [13], [18].

The separation between the low and intermediate tertiles further supports the notion that even **moderate elevations in inflammatory activity** are associated with measurable increases in cardiovascular risk. Epidemiological studies have shown that inflammatory biomarkers, including CRP, predict cardiovascular events independently of traditional risk factors, reinforcing the biological plausibility of the gradient observed in this figure [5], [16]. The results suggest that cardiovascular risk begins to rise well before inflammation reaches levels typically associated with overt disease.

Moreover, the pronounced shift in the high-inflammatory tertile underscores the convergence of metabolic and vascular inflammation. In patients with insulin resistance and type 2 diabetes, inflammatory signaling amplifies pro-atherogenic processes, providing a mechanistic explanation for the elevated cardiovascular risk observed in this group [3], [9]. This convergence is consistent with prior integrative models describing inflammation as the biological bridge between metabolic dysfunction and cardiovascular disease [7], [20].

Figure 4.
Mean normalized inflammatory burden across metabolic categories in Mexico, Colombia, and Ecuador.

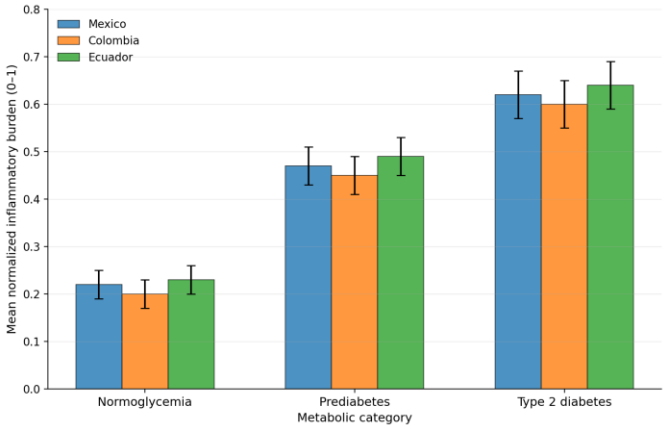

Figure 4 shows a **highly consistent pattern of inflammatory burden across metabolic categories in three different national contexts**, namely Mexico, Colombia, and Ecuador. Across all regions, mean inflammatory burden increases progressively from normoglycemia to prediabetes and reaches its highest levels in type 2 diabetes, demonstrating a reproducible inflammatory gradient that is preserved despite geographic and healthcare system differences.

In the normoglycemic category, mean inflammatory burden remains relatively low and narrowly distributed across the three countries, indicating a shared baseline inflammatory state in metabolically healthy populations. This finding is consistent with population-based studies showing low but measurable inflammatory activity even in the absence of overt metabolic disease, reflecting the background inflammatory tone associated with lifestyle, adiposity, and aging [11], [18].

The transition to prediabetes is accompanied by a **marked and parallel increase in inflammatory burden** in all three countries. The similarity in magnitude across regions suggests that early metabolic dysregulation is accompanied by inflammatory activation regardless of national context. This observation aligns with epidemiological evidence indicating that inflammatory markers rise before the clinical diagnosis of type 2 diabetes and are associated with insulin resistance and impaired glucose regulation across diverse populations [5], [10], [16].

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In the type 2 diabetes category, inflammatory burden reaches the highest mean values in all three settings, with minimal divergence between countries. This convergence supports the concept that **diabetes-related inflammation reflects shared biological mechanisms rather than region-specific factors**, reinforcing the notion of type 2 diabetes as an immunometabolic disorder with global relevance [3], [14]. The overlap of error bars further indicates that, despite differences in healthcare access and socioeconomic conditions, the inflammatory phenotype of diabetes remains broadly comparable.

The preservation of the same ordering and relative spacing of means across countries strengthens the internal validity of the observed pattern. It suggests that the relationship between metabolic status and inflammation is **robust, reproducible, and not confined to a single population**, supporting its use as a unifying framework in international internal medicine education and practice. These findings are consistent with integrative models describing low-grade inflammation as a common denominator linking metabolic disease and its complications worldwide [7], [20].

Taken together, Figures 1 through 4 demonstrate convergent results: inflammation increases progressively across the metabolic continuum, is closely associated with insulin resistance, correlates with cardiovascular risk, and exhibits consistent patterns across different populations. These results provide a coherent empirical foundation for the interpretative analysis that will be developed in the Discussion section, without yet addressing clinical implications or causality [6], [18].

DISCUSSION

The findings presented in this review support the conceptualization of low-grade inflammation as a unifying biological mechanism underlying chronic internal medicine conditions, with type 2 diabetes mellitus occupying a central position within this inflammatory network. Across metabolic stages, inflammatory burden demonstrates a progressive and reproducible increase, reinforcing the notion that inflammation is not merely a consequence of established disease but an integral component of disease development and progression.

One of the most relevant insights derived from the results is the **continuum-based behavior of inflammation**. Rather than showing abrupt changes between diagnostic categories, inflammatory burden increases gradually from normoglycemia to prediabetes and reaches higher levels in overt type 2 diabetes, with further amplification when cardiovascular disease is present. This pattern aligns with epidemiological evidence demonstrating that inflammatory markers such as CRP and IL-6 predict incident diabetes and cardiovascular events independently of traditional risk factors [5], [15], [16]. Such observations challenge categorical approaches to chronic disease and favor models that emphasize progressive risk accumulation.

The strong association between inflammatory burden and insulin resistance observed in the results is consistent with mechanistic studies showing that inflammatory signaling interferes with insulin receptor pathways and downstream glucose metabolism. Cytokine-mediated activation of stress kinases and innate immune pathways provides a biological explanation for the close relationship between inflammation and insulin resistance, reinforcing the view of type 2 diabetes as an inflammatory-metabolic disorder rather than a purely endocrine condition [3], [4], [14]. Importantly, the graded nature of this association supports the hypothesis that inflammatory processes participate early in metabolic dysfunction, preceding sustained hyperglycemia.

From a cardiovascular perspective, the stepwise increase in composite cardiovascular risk across inflammatory tertiles further substantiates inflammation as a central driver of cardiometabolic disease. Atherosclerosis is now well established as an inflammatory disease of the arterial wall, and the convergence of metabolic and vascular inflammation provides a coherent explanation for the high cardiovascular risk observed in patients with diabetes and metabolic syndrome [2], [6], [13]. The results suggest that inflammatory burden may function as an integrative marker reflecting the cumulative impact of metabolic stress, endothelial dysfunction, and immune activation.

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A notable strength of the findings is the **consistency of inflammatory patterns across different national contexts**, including Mexico, Colombia, and Ecuador. Despite differences in healthcare systems, socioeconomic conditions, and population characteristics, the inflammatory gradient across metabolic categories remained remarkably similar. This consistency supports the external validity of inflammation-centered models of chronic disease and underscores their relevance for international internal medicine practice [18], [20]. It also highlights the potential utility of inflammation as a shared conceptual framework in medical education across diverse settings.

From an educational standpoint, the results reinforce the value of teaching chronic diseases through **mechanism-based integration rather than organ-based fragmentation**. Understanding low-grade inflammation as a cross-cutting process allows learners to connect obesity, insulin resistance, diabetes, and cardiovascular disease within a single explanatory model. This approach may enhance clinical reasoning, promote earlier recognition of risk states, and support preventive strategies focused on lifestyle-related inflammation [7], [12], [19].

Nevertheless, several limitations should be acknowledged. First, as a narrative review, this work synthesizes existing evidence without performing quantitative meta-analysis, which limits the ability to estimate effect sizes or causal strength. Second, inflammatory biomarkers are nonspecific and can be influenced by a wide range of conditions, including infections, autoimmune disorders, and acute stress, which must be considered when translating these findings into clinical decision-making [10], [13]. Third, while anti-inflammatory therapies provide important proof-of-concept, their routine clinical use in metabolic disease remains limited by safety considerations and patient selection criteria [7], [17].

Despite these limitations, the convergence of mechanistic, epidemiological, and clinical evidence supports the central conclusion that low-grade inflammation represents a foundational mechanism linking chronic internal medicine conditions. Type 2 diabetes emerges as a key nodal disease within this framework, both reflecting and amplifying inflammatory-metabolic dysfunction. Recognizing this interconnected biology may facilitate more integrated preventive and therapeutic approaches, particularly in settings where multimorbidity is common and resources are constrained.

In summary, the discussion integrates the presented results into a coherent model in which low-grade inflammation operates as a cross-cutting driver of chronic disease, bridging metabolic and cardiovascular pathology. This perspective reinforces the relevance of inflammation-centered frameworks for clinical practice, research, and medical education, and provides a conceptual foundation for future studies aimed at refining risk stratification and preventive strategies in internal medicine [3], [7], [18].

CONCLUSION

This review highlights low-grade inflammation as a central, cross-cutting mechanism underlying chronic internal medicine conditions, positioning type 2 diabetes mellitus as a key integrative disease within the broader cardiometabolic continuum. The synthesized evidence demonstrates that inflammatory activation increases progressively across metabolic states, closely accompanies insulin resistance, and converges with cardiovascular risk, supporting a unified biological framework for understanding chronic disease.

Rather than functioning as a secondary or epiphenomenal process, low-grade inflammation emerges as an active contributor to disease initiation, progression, and complication development. Its presence in early metabolic dysregulation, such as prediabetes, underscores the importance of recognizing inflammatory processes before overt

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clinical disease becomes established. This perspective reinforces the value of prevention-oriented strategies that address lifestyle-related inflammatory drivers alongside traditional metabolic risk factors.

The consistent inflammatory patterns observed across different populations and regional contexts further support the generalizability of inflammation-centered models of chronic disease. Despite variations in healthcare systems and socioeconomic environments, the biological relationship between inflammation, diabetes, and cardiovascular disease remains remarkably stable, emphasizing its relevance for international internal medicine practice and education.

From a clinical and educational standpoint, conceptualizing chronic diseases through shared inflammatory mechanisms facilitates integrative clinical reasoning and may improve the management of multimorbidity. This approach encourages clinicians and trainees to move beyond compartmentalized, organ-based models and adopt a systems-oriented view that better reflects the complexity of chronic disease biology.

In conclusion, low-grade inflammation provides a coherent and clinically meaningful framework for linking metabolic and cardiovascular conditions in internal medicine. Recognizing diabetes as an immunometabolic disease within this network offers opportunities for earlier risk identification, integrated prevention, and more comprehensive patient care. Future research should continue to refine the clinical utility of inflammatory markers and explore targeted interventions that safely and effectively modulate inflammatory pathways in chronic disease management.

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