Integración del Inmunometabolismo y la Inflamación Crónica: Un Enfoque Basado en Sistemas para la Multimorbilidad en Medicina Interna

Integrating Immunometabolism and Chronic Inflammation: A Systems-Based Approach to Multimorbidity in Internal Medicine

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RESUMEN

Las enfermedades crónicas en medicina interna han sido tradicionalmente abordadas como entidades aisladas; sin embargo, la evidencia actual respalda su interpretación como procesos interconectados sostenidos por redes metabólico-inflamatorias. El objetivo de esta revisión fue analizar e integrar evidencia de alto impacto sobre inmunometabolismo, inflamación crónica y

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disfunción sistémica para proponer un marco basado en sistemas aplicable a la práctica clínica y la educación médica. Se realizó una revisión narrativa estructurada utilizando 20 referencias científicas indexadas en bases de datos biomédicas. El análisis se centró en mecanismos clave como metaflamación, resistencia a la insulina, inflamación del tejido adiposo, disfunción vascular, microbiota intestinal, señalización del músculo esquelético y cambios inflamatorios asociados al envejecimiento. Los resultados demostraron una convergencia consistente entre mecanismos, sistemas biológicos y dominios clínicos, destacando la inflamación crónica como eje central que conecta obesidad, diabetes tipo 2, aterosclerosis y multimorbilidad. Además, se identificó que estos procesos están modulados por factores de estilo de vida, ambiente y envejecimiento. La integración de estos hallazgos respalda un modelo de enfermedad basado en redes que supera el enfoque tradicional por órganos. Este marco ofrece beneficios en el razonamiento clínico, la estratificación de riesgo, la prevención y la educación médica, especialmente en contextos como México, Colombia y Ecuador. En conclusión, las redes metabólico-inflamatorias constituyen un principio fundamental para comprender la enfermedad crónica en la medicina interna moderna.

PALABRAS CLAVE

inmunometabolismo, inflamación crónica, metaflamación, resistencia a la insulina, obesidad, síndrome metabólico, aterosclerosis, multimorbilidad, microbiota intestinal, inflammaging, medicina interna, medicina basada en sistemas

ABSTRACT

Chronic diseases in internal medicine have traditionally been approached as isolated entities; however, emerging evidence supports their interpretation as interconnected processes sustained by metabolic–inflammatory networks. This review aimed to analyze and integrate current high-impact evidence on immunometabolism, chronic inflammation, and systemic dysregulation in order to propose a systems-based framework applicable to clinical practice and medical education. A structured narrative review was conducted using 20 peer-reviewed references indexed in major biomedical databases. The analysis focused on key mechanisms including metaflammation, insulin resistance, adipose tissue inflammation, vascular dysfunction, gut microbiota interactions, skeletal muscle signaling, and ageing-related inflammatory changes. The results demonstrated a consistent convergence across mechanistic, biological, and clinical domains, highlighting chronic inflammation as a central driver linking obesity, type 2 diabetes mellitus, atherosclerosis, and multimorbidity. Furthermore, the evidence revealed that these processes are dynamically influenced by lifestyle factors, environmental exposures, and ageing. The integration of these findings supports a network-based model of disease that transcends traditional organ-specific approaches. This framework offers potential benefits in clinical reasoning, risk stratification, preventive strategies, and medical education, particularly in regions with a high burden of chronic disease such as Mexico, Colombia, and Ecuador. In conclusion, metabolic–inflammatory networks represent a fundamental organizing principle in chronic disease, providing a coherent and clinically relevant perspective for modern internal medicine.

KEYWORDS

immunometabolism, chronic inflammation, metaflammation, insulin resistance, obesity, metabolic syndrome, atherosclerosis, multimorbidity, gut microbiota, inflammaging, internal medicine, systems-based medicine

INTRODUCCIÓN

Over the past decades, internal medicine has undergone a profound transformation driven by the increasing recognition that chronic diseases are not isolated entities but rather interconnected processes sustained by complex metabolic and inflammatory networks. Conditions such as type 2 diabetes mellitus, atherosclerosis, obesity, chronic kidney disease, and non-alcoholic fatty liver disease share common pathophysiological pathways characterized by persistent low-grade inflammation and metabolic dysregulation. This paradigm shift has given rise to the concept of *immunometabolism*, which integrates immune responses with metabolic homeostasis as a central framework for understanding chronic disease progression (Hotamisligil, 2017; O'Neill et al., 2016).

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Chronic inflammation has been identified as a unifying mechanism underlying a wide spectrum of non-communicable diseases, significantly contributing to morbidity and mortality worldwide. Unlike acute inflammation, which is protective and self-limited, chronic low-grade inflammation—often referred to as "metaflammation"—persists over time and disrupts normal cellular and systemic functions (Furman et al., 2019; Gregor & Hotamisligil, 2011). This inflammatory state is closely associated with metabolic stressors such as excess nutrient intake, adipose tissue expansion, mitochondrial dysfunction, and alterations in gut microbiota composition (Tilg et al., 2020; Scheithauer et al., 2020). Consequently, metabolic-inflammatory interactions are now considered central to the pathogenesis of many chronic diseases traditionally managed within internal medicine.

The relevance of this topic is particularly evident in the current global epidemiological context. Non-communicable diseases account for the majority of deaths worldwide, with a disproportionate burden observed in low- and middle-income countries, including regions of Latin America such as Mexico, Colombia, and Ecuador. In these settings, rapid urbanization, dietary transitions, and sedentary lifestyles have accelerated the prevalence of metabolic disorders, while healthcare systems face increasing challenges in managing multimorbidity (Franceschi et al., 2018; Libby, 2021). The coexistence of multiple chronic conditions in a single patient underscores the need for a systems-based approach that transcends traditional organ-specific models of care.

Previous research has extensively documented the molecular and cellular mechanisms linking metabolism and inflammation. For instance, adipose tissue is now recognized as an active endocrine organ capable of secreting pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which contribute to insulin resistance and systemic inflammation (Saltiel & Olefsky, 2017; Reilly & Saltiel, 2017). Similarly, the role of innate immunity in metabolic disease has been highlighted through the activation of inflammasomes and pattern recognition receptors in response to metabolic stress signals (Kotas & Medzhitov, 2015). These mechanisms provide a biological basis for understanding how metabolic disturbances translate into chronic inflammatory states.

In parallel, advances in cardiovascular research have reinforced the central role of inflammation in atherosclerosis, shifting the focus from lipid accumulation alone to immune-mediated vascular injury. Clinical and translational studies have demonstrated that targeting inflammatory pathways, such as the interleukin-1 and interleukin-6 axes, may reduce cardiovascular risk independently of lipid levels (Ridker, 2016; Libby, 2021). Likewise, type 2 diabetes has been redefined not only as a metabolic disorder but also as an inflammatory condition, where immune-mediated mechanisms contribute to β-cell dysfunction and insulin resistance (Donath & Shoelson, 2011; DeFronzo et al., 2015).

Emerging evidence also highlights the critical role of the gut microbiota in modulating metabolic and inflammatory processes. Dysbiosis has been associated with increased intestinal permeability, endotoxemia, and activation of systemic inflammatory pathways, thereby linking environmental factors with host metabolic responses (Tilg et al., 2020; Scheithauer et al., 2020). Additionally, skeletal muscle has been recognized as a key regulator of systemic metabolism through the secretion of myokines, further illustrating the integrative nature of metabolic-inflammatory networks (Pedersen & Febbraio, 2012).

Despite these advances, current clinical practice in internal medicine often remains fragmented, with diseases managed in isolation rather than as components of a broader systemic network. This gap highlights the need for a conceptual framework that integrates metabolic and inflammatory pathways into a unified model of disease. Such an approach could improve diagnostic accuracy, facilitate early identification of high-risk patients, and promote more effective therapeutic strategies.

The present review aims to synthesize current evidence on metabolic-inflammatory networks in chronic disease and propose a comprehensive framework for internal medicine practice. The central question guiding this work is how the integration of immunometabolic mechanisms can enhance the understanding and management of chronic diseases across different organ systems. This review is based on a structured analysis of high-impact literature, including foundational and recent studies indexed in major biomedical databases, ensuring the inclusion of robust and clinically relevant evidence.

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The methodological approach of this review involves the identification, selection, and synthesis of key studies addressing the interaction between metabolic and inflammatory pathways. Emphasis was placed on seminal contributions and recent advances that have shaped the current understanding of immunometabolism, as well as on studies with translational and clinical implications. By aligning the selection of evidence with the central research question, this review seeks to provide a coherent and clinically applicable perspective.

Furthermore, this work adopts an international perspective, incorporating insights relevant to diverse healthcare contexts, particularly in Latin American countries such as Mexico, Colombia, and Ecuador. These regions share common epidemiological challenges related to chronic diseases, making them particularly suitable for the application of integrated, systems-based approaches in internal medicine.

DESARROLLO

The growing prevalence of chronic disease has exposed the limitations of reductionist models in internal medicine, particularly those that interpret metabolic disorders, cardiovascular disease, chronic kidney injury, and age-related multisystem deterioration as separate and unrelated processes. A more robust interpretation of current evidence suggests that many of these conditions are sustained by overlapping metabolic–inflammatory circuits, in which nutrient excess, cellular stress, immune activation, endocrine signaling, microbiome alterations, and tissue remodeling act in a coordinated and self-reinforcing manner. From this perspective, chronic disease is better understood not as the sum of isolated diagnoses, but as the expression of a disturbed biological network that evolves over time and across organs (Hotamisligil, 2017; O'Neill et al., 2016).

One of the strongest foundations for this framework is the recognition that chronic low-grade inflammation is not merely a consequence of disease, but often an active driver of pathogenesis. Furman et al. (2019) described chronic inflammation as a cross-cutting mechanism in diseases throughout the lifespan, emphasizing that inflammatory signaling becomes maladaptive when sustained over time. This concept is especially relevant in internal medicine, where patients frequently present with multimorbidity rather than with a single disease entity. In these individuals, inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha, interleukin-1β, chemokines, and acute-phase proteins do not remain confined to one organ system; instead, they contribute to systemic metabolic dysfunction, endothelial injury, insulin resistance, immune dysregulation, and progressive tissue damage (Furman et al., 2019; Ridker, 2016).

The concept of **metaflammation**, introduced and expanded in immunometabolic research, is particularly useful in understanding this phenomenon. Hotamisligil (2017) described metaflammation as a chronic, sterile, low-grade inflammatory response triggered by excess nutrients and metabolic stress. Unlike classical inflammation induced by infection or trauma, metaflammation originates from persistent energy imbalance, lipotoxicity, oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction. This chronic inflammatory condition helps explain why obesity, type 2 diabetes, metabolic syndrome, and atherosclerosis often cluster in the same patient and share common biological pathways. In this sense, the internal medicine clinician is not dealing with unrelated disorders, but with distinct clinical expressions of the same network disturbance.

Adipose tissue occupies a central place in this network. It is no longer regarded as a passive storage site for energy, but as a metabolically active and immunologically competent organ. In obesity, adipocyte hypertrophy is accompanied by hypoxia, altered adipokine secretion, macrophage infiltration, and enhanced production of pro-inflammatory cytokines. Saltiel and Olefsky (2017) explained that inflamed adipose tissue becomes a source of systemic signals that interfere with insulin action in muscle, liver, and vascular tissues. Reilly and Saltiel (2017) further showed that adipose inflammation represents both an adaptive and maladaptive response: initially, it may help tissue remodeling under caloric excess, but over time it promotes insulin resistance, fibrosis, and systemic metabolic instability. Gregor and Hotamisligil (2011) also emphasized that the inflammatory environment within adipose depots is shaped by immune cell recruitment and stress signaling pathways, reinforcing the notion that obesity is, in part, an immunologic disease.

These findings are particularly relevant because insulin resistance is one of the clearest bridges between metabolism and inflammation. Tilg and Moschen (2010) argued that inflammatory mediators impair insulin receptor signaling and alter glucose homeostasis through complex intracellular mechanisms involving serine phosphorylation pathways,

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Revista IECCMEXICO

stress kinases, and transcriptional dysregulation. Donath and Shoelson (2011) reframed type 2 diabetes mellitus as an inflammatory disease in which β-cell dysfunction and insulin resistance are amplified by innate immune activation. Pickup (2004), in an earlier but still influential contribution, proposed that activated innate immunity is deeply involved in the pathogenesis of type 2 diabetes, thereby anticipating the broader immunometabolic model that now dominates the field. Later, DeFronzo et al. (2015) integrated these insights into a broader pathophysiologic view of type 2 diabetes, showing that hyperglycemia emerges from multiple interacting defects rather than from a single abnormality. This is highly relevant to internal medicine because it justifies why successful management requires not only glycemic control, but also recognition of inflammatory burden, body composition, cardiovascular risk, renal vulnerability, and behavior-related determinants.

Cardiovascular disease provides another compelling example of the metabolic–inflammatory continuum. Atherosclerosis was once understood primarily as a lipid storage disorder, but contemporary evidence has repositioned it as a chronic inflammatory disease of the arterial wall. Libby (2021) described the modern landscape of atherosclerosis as one in which immune mechanisms, endothelial dysfunction, lipid handling, and vascular inflammation interact dynamically. Ridker (2016) traced the scientific transition from C-reactive protein as a biomarker to interleukin-6 and interleukin-1 as upstream inflammatory mediators and potential therapeutic targets. This evolution is critical because it demonstrates that the inflammatory component of chronic disease is not merely descriptive; it has prognostic and therapeutic implications. For internal medicine, this means that a patient with central obesity, prediabetes, elevated inflammatory markers, and dyslipidemia should not be viewed through separate cardiology, endocrinology, and nutrition lenses alone. Rather, these features should be interpreted as linked manifestations of a shared pathobiological process.

The role of innate immunity further strengthens this integrated view. O'Neill et al. (2016) offered a practical conceptual guide to immunometabolism, explaining that immune cells and metabolic pathways are deeply interdependent. Macrophages, T cells, dendritic cells, and other immune populations modify their phenotype according to nutrient availability, oxygen tension, mitochondrial activity, and metabolic substrate utilization. At the same time, these cells influence systemic energy homeostasis through cytokine production and tissue-specific effects. Kotas and Medzhitov (2015) added that homeostasis and inflammation are not opposing states but biologically intertwined responses to internal and external stress. Their work is especially important in internal medicine because many chronic conditions emerge when adaptive homeostatic responses become persistent and maladaptive. Thus, disease susceptibility is shaped not only by genetics or external exposures, but also by how the organism regulates inflammatory and metabolic balance over time.

An evolutionary interpretation helps explain why these mechanisms are so pervasive. Wang et al. (2019) argued that immunometabolic pathways evolved to optimize survival in environments characterized by intermittent food scarcity, infectious threats, and fluctuating energy demands. Under those conditions, inflammatory activation and energy conservation could be beneficial. However, in contemporary societies marked by caloric excess, physical inactivity, circadian disruption, environmental stress, and long life expectancy, those same pathways may become pathogenic. This evolutionary mismatch is especially relevant in Latin America, where rapid urbanization and nutritional transitions have occurred alongside persistent social inequality and uneven access to preventive care. In countries such as Mexico, Colombia, and Ecuador, internal medicine increasingly faces patients whose disease patterns reflect both biological vulnerability and structural determinants of health. The metabolic–inflammatory framework is therefore clinically useful not only at the molecular level, but also as a lens for understanding how social change becomes biologically embodied.

The intestinal microbiota has emerged as one of the most influential modulators of this network. Tilg et al. (2020) showed that the gut microbiota can fuel metabolic inflammation through mechanisms involving microbial metabolites, intestinal permeability, endotoxemia, and immune activation. Scheithauer et al. (2020) further explained that dysbiosis may function as a trigger for obesity-related inflammation and type 2 diabetes by disturbing host–microbe communication and mucosal integrity. These insights are significant because they connect diet, lifestyle, and environmental exposure with systemic inflammatory responses in a biologically plausible manner. For the practicing internist, the implication is clear: gastrointestinal, metabolic, endocrine, and immune processes should not be treated

Edition 4, Year 3, Number 1, 2026
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IECCMEXICO Review

as separate spheres. A patient's nutritional pattern, antibiotic exposure, obesity phenotype, and chronic inflammatory profile may all be part of the same causal chain.

Muscle tissue also participates actively in this network. Pedersen and Febbraio (2012) demonstrated that skeletal muscle acts as a secretory organ capable of releasing myokines that influence glucose metabolism, lipid utilization, inflammation, and inter-organ communication. This observation reinforces the clinical importance of physical activity beyond its traditional role in calorie expenditure. Exercise modifies inflammatory tone, improves insulin sensitivity, preserves muscle quality, and affects systemic metabolic adaptation. From an internal medicine standpoint, this is particularly valuable because it supports non-pharmacologic treatment not as an adjunctive or secondary measure, but as a biologically grounded intervention capable of modifying central disease mechanisms.

Ageing introduces an additional layer of complexity. Franceschi et al. (2018) described the concept of **inflammaging**, referring to the chronic, low-level inflammatory state that accompanies ageing and contributes to age-related diseases. This immune–metabolic perspective is crucial in internal medicine, where elderly patients often exhibit overlapping syndromes such as frailty, sarcopenia, diabetes, atherosclerosis, cognitive decline, and renal dysfunction. In these patients, disease expression cannot be fully understood through organ-specific categories alone. Instead, inflammaging suggests that the cumulative burden of metabolic stress, immune activation, senescent cell signaling, and impaired repair processes creates a shared biological terrain on which multiple chronic diseases develop. Furman et al. (2019) support this broader view by emphasizing that chronic inflammation is a life-course process with implications for both early and late disease expression.

Dietary patterns are another major determinant of inflammatory state. Calder et al. (2011) reviewed the association between nutrition and low-grade inflammation, showing that dietary composition can either amplify or reduce inflammatory signaling related to overweight and obesity. This is highly relevant in countries undergoing nutrition transition, where increased consumption of ultra-processed foods, sugar-sweetened beverages, and energy-dense diets contributes to both obesity and inflammation. In internal medicine, dietary history must therefore be interpreted not only in terms of calories or body weight, but also in terms of inflammatory potential and its interaction with comorbid disease. The same logic applies to central obesity, hepatic steatosis, hypertriglyceridemia, and insulin resistance, all of which can be understood as nodes within the same metabolic–inflammatory network.

Although some of the cited studies focus on individual disease categories, the strength of the current framework lies in integration. Internal medicine is uniquely positioned to benefit from this perspective because its clinical practice routinely involves diagnostic uncertainty, multimorbidity, and longitudinal follow-up. A network-based model allows the physician to identify recurring pathophysiological themes across different diagnoses. For example, a patient with obesity, hypertension, chronic kidney disease, dyslipidemia, and impaired fasting glucose may be experiencing progressive network failure characterized by adipose inflammation, endothelial dysfunction, renin–metabolic crosstalk, mitochondrial stress, and gut-derived inflammatory signaling. The apparent diversity of diagnoses may conceal a smaller number of shared biological drivers.

This has practical implications for risk stratification and treatment. If chronic diseases share inflammatory and metabolic roots, then interventions may have effects across organ systems. Weight reduction, physical activity, dietary improvement, and sleep regulation may decrease inflammatory burden and improve glucose metabolism, vascular health, hepatic function, and quality of life simultaneously. Similarly, pharmacologic strategies aimed at upstream mediators may provide broader benefits than those aimed only at downstream manifestations. Ridker (2016) and Libby (2021) suggest this clearly in the cardiovascular field, while Donath and Shoelson (2011) and DeFronzo et al. (2015) provide parallel reasoning in diabetes. In clinical practice, the implication is that internal medicine must increasingly combine disease-specific treatment with mechanism-oriented thinking.

This approach also supports medical education. If students are trained to recognize chronic disease through metabolic–inflammatory networks, they may develop a deeper and more coherent understanding of internal medicine. Instead of memorizing separate disease pathways, they can learn to identify recurring principles: energy imbalance, tissue stress, immune activation, impaired signaling, maladaptive repair, organ cross-talk, and progressive system failure. Such training may be especially useful in Latin American educational settings, including Mexico, Colombia, and Ecuador, where future internists will frequently encounter patients with multimorbidity, obesity-related disorders, chronic

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IECCMEXICO Review

vascular risk, and limited access to highly specialized fragmented care. A systems-based conceptual model may therefore improve not only scientific understanding, but also diagnostic reasoning, therapeutic prioritization, and continuity of care.

At the international level, this framework is relevant because chronic non-communicable diseases have become the dominant burden of adult medicine across very different healthcare environments. The biological mechanisms described in high-impact literature remain broadly applicable, but their clinical expression is shaped by local realities such as food systems, socioeconomic inequality, urban design, healthcare access, cultural behaviors, and epidemiologic transition. In Mexico, Colombia, and Ecuador, the interaction between rising metabolic disease and health system constraints makes integrated internal medicine particularly necessary. The metabolic–inflammatory model offers a conceptual bridge between molecular science and real-world medicine, allowing clinicians and educators to connect biological evidence with patient complexity in diverse contexts.

In summary, the current evidence strongly supports the idea that chronic diseases in internal medicine are sustained by interdependent metabolic and inflammatory networks rather than by isolated organ-specific mechanisms. Adipose tissue inflammation, insulin resistance, innate immune activation, vascular inflammation, gut microbiota disruption, muscle signaling, diet-related inflammatory load, and ageing-related immune dysregulation all participate in a shared pathophysiological landscape (Hotamisligil, 2017; Gregor & Hotamisligil, 2011; O'Neill et al., 2016; Franceschi et al., 2018; Tilg et al., 2020). Understanding this landscape is essential for modern internal medicine because it improves conceptual clarity, supports integrated care, and offers a biologically coherent framework for teaching, research, and clinical decision-making.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To **analyze and integrate** current evidence on metabolic–inflammatory networks in chronic diseases in order to **propose a systems-based framework** applicable to internal medicine practice and medical education in diverse clinical contexts, including Latin America.

Specific Objectives

Cognitive Domain

1. To **identify** the main metabolic and inflammatory pathways involved in chronic diseases, including insulin resistance, adipose tissue inflammation, vascular inflammation, and immunometabolic signaling.
2. To **describe** the interaction between immune mechanisms and metabolic processes in the development of conditions such as type 2 diabetes, atherosclerosis, and obesity.
3. To **analyze** the role of key biological systems—such as adipose tissue, gut microbiota, skeletal muscle, and the innate immune system—in the regulation of systemic inflammation.
4. To **compare** traditional organ-based models of internal medicine with systems-based approaches focused on metabolic–inflammatory networks.
5. To **evaluate** the clinical implications of immunometabolism in the diagnosis, risk stratification, and management of chronic diseases.

Psychomotor Domain

6. To **apply** a systems-based approach in the clinical assessment of patients with multimorbidity, integrating metabolic and inflammatory components into diagnostic reasoning.
7. To **integrate** clinical, biochemical, and epidemiological data to identify patterns consistent with metabolic–inflammatory dysfunction.
8. To **demonstrate** the ability to interpret laboratory markers related to inflammation and metabolism (e.g., glucose, lipid profile, inflammatory markers) within a unified clinical framework.
9. To **implement** evidence-based strategies (lifestyle and pharmacologic) targeting shared pathophysiological mechanisms across multiple chronic conditions.

Affective Domain

10. To **recognize** the importance of a holistic and patient-centered approach in the management of chronic diseases.
11. To **value** interdisciplinary collaboration in addressing complex metabolic–inflammatory conditions.
12. To **promote** critical thinking toward traditional disease classification and encourage openness to integrative models in internal medicine.
13. To **appreciate** the relevance of sociocultural and regional factors in shaping the epidemiology and management of chronic diseases in countries such as Mexico, Colombia, and Ecuador.
14. To **encourage** continuous learning and adaptation to emerging evidence in immunometabolism and chronic disease management.

OBJETO DE ESTUDIO

The object of study of this review is the **metabolic–inflammatory network underlying chronic non-communicable diseases**, understood as a complex, dynamic, and interconnected biological system that integrates metabolic dysregulation and immune activation across multiple organ systems.

This phenomenon encompasses the interaction between key physiological components, including **adipose tissue, skeletal muscle, liver, vascular endothelium, immune cells, and gut microbiota**, all of which contribute to the initiation, maintenance, and progression of chronic diseases. These interactions are mediated through molecular pathways involving cytokines, adipokines, inflammatory mediators, metabolic substrates, and intracellular signaling cascades that collectively define the state of systemic inflammation and metabolic imbalance (Hotamisligil, 2017; O'Neill et al., 2016).

From a clinical perspective, the object of study focuses on **adult patients with chronic diseases commonly managed in internal medicine**, particularly those presenting with conditions such as type 2 diabetes mellitus, obesity, atherosclerosis, metabolic syndrome, and related comorbidities. These patients frequently exhibit **multimorbidity**, where multiple conditions coexist and interact, reflecting a shared pathophysiological substrate rather than independent disease processes (Furman et al., 2019; Libby, 2021).

At a population level, this study is framed within **diverse healthcare contexts**, with particular relevance to Latin American regions such as Mexico, Colombia, and Ecuador, where the epidemiological transition has led to a rising burden of chronic metabolic diseases. In these settings, environmental, nutritional, socioeconomic, and healthcare access factors interact with biological mechanisms, influencing both disease expression and clinical outcomes (Franceschi et al., 2018).

Conceptually, the object of study is not limited to isolated diseases but rather to the **network-based model of disease**, in which chronic conditions are interpreted as interconnected manifestations of systemic dysregulation. This includes processes such as chronic low-grade inflammation (metaflammation), insulin resistance, endothelial dysfunction, immune system activation, microbiota alterations, and age-related inflammatory changes (inflammaging), all of which are central to the evolution of chronic disease (Tilg et al., 2020; Scheithauer et al., 2020).

METOLOLOGÍA

This study was designed as a **narrative review with a structured scientific method approach**, aimed at analyzing and integrating current evidence on metabolic–inflammatory networks in chronic disease and their relevance to internal medicine practice. The methodological structure was selected to ensure conceptual clarity, reproducibility, and coherence between the research question, the review process, and the educational and clinical objectives of the article.

The **scientific method** was chosen as the guiding methodology because it provides an organized sequence for identifying a problem, formulating a guiding question, collecting evidence, critically analyzing available information, and generating a reasoned interpretation applicable to clinical and academic settings. In the context of this review, the scientific method was adapted to the logic of evidence synthesis rather than experimental intervention, allowing the study to maintain analytical rigor while remaining appropriate for a review article.

1. Identification of the problem

The first methodological step consisted of identifying the central problem addressed by this review: the persistent fragmentation of chronic disease management in internal medicine despite growing evidence that many chronic conditions share common metabolic–inflammatory mechanisms. Although obesity, type 2 diabetes mellitus, atherosclerosis, and other chronic disorders are often approached as separate clinical entities, the literature increasingly supports the existence of overlapping pathways involving immune activation, insulin resistance, endothelial dysfunction, adipose inflammation, microbiota-related signaling, and ageing-associated inflammatory change. This discrepancy between scientific knowledge and routine clinical reasoning justified the development of the present review.

2. Formulation of the research question

Once the problem had been defined, the review was guided by the following research question: **How can current evidence on metabolic–inflammatory networks in chronic diseases be integrated into a systems-based framework for internal medicine practice and medical education?**

This guiding question was broad enough to include molecular, physiological, clinical, and educational dimensions, but sufficiently focused to orient the selection and interpretation of literature. It also aligned with the general objective of the study, which was to analyze and integrate available evidence in order to support a more comprehensive model of chronic disease in internal medicine.

3. Literature selection strategy

The documentary corpus of this review was based on **20 high-impact academic references**, primarily indexed in PubMed and published in internationally recognized journals in the fields of internal medicine, immunology, endocrinology, metabolism, cardiology, and translational science. These references were selected because of their scientific relevance, conceptual influence, and direct contribution to the understanding of metabolic–inflammatory interactions in chronic disease.

The selection process prioritized publications that met the following criteria:

- Studies and reviews focused on **chronic inflammation**, **immunometabolism**, **metaflammation**, **inflammaging**, **insulin resistance**, **atherosclerosis**, **obesity-related inflammation**, **gut microbiota**, and related systemic mechanisms.
- Articles published in **high-impact journals** with broad international recognition.
- References with clear relevance to the clinical and conceptual field of **internal medicine**.
- Studies that offered either **foundational theoretical frameworks** or **recent integrative perspectives** on chronic disease mechanisms.
- Articles with valid and correctly cited DOI identifiers.

The review was intentionally centered on these 20 references in order to maintain thematic consistency and to ensure that all sections of the manuscript were developed from a defined and coherent bibliographic base.

4. Data extraction and organization

After selecting the references, the relevant content from each source was extracted and organized according to thematic categories. The extraction process focused on identifying the main concepts, mechanisms, and clinical implications discussed in each article. For the purposes of this review, the information was grouped into the following analytical axes:

- Conceptual foundations of chronic inflammation and immunometabolism
- Adipose tissue and obesity-related inflammatory signaling
- Insulin resistance and type 2 diabetes as inflammatory-metabolic disorders
- Vascular inflammation and atherosclerosis
- Gut microbiota and intestinal drivers of metabolic inflammation
- Skeletal muscle as a metabolic and signaling organ

- Ageing, inflammaging, and multisystem chronic disease
- Clinical and educational implications for internal medicine

This thematic organization allowed the evidence to be interpreted not as isolated findings, but as parts of a broader biological and clinical network.

5. Critical analysis of the evidence

The selected literature was then subjected to a process of **qualitative critical analysis**, in which the main arguments, recurring mechanisms, and converging interpretations across studies were identified. Rather than limiting the review to a descriptive summary of individual articles, the analysis emphasized conceptual integration. This step aimed to detect common pathophysiological patterns linking chronic diseases traditionally classified under different specialties.

Particular attention was given to the relationship between metabolic dysregulation and inflammatory activation, as well as to the clinical implications of viewing these interactions through a systems-based lens. The review did not attempt to quantify pooled outcomes or perform meta-analytic calculations, since its purpose was interpretative and conceptual rather than statistical. However, it maintained methodological discipline by restricting the analysis to the selected references and by grounding all major arguments in the reviewed literature.

6. Synthesis and construction of the interpretive framework

The final methodological step consisted of synthesizing the analyzed evidence into an interpretive framework applicable to internal medicine. This synthesis was based on the premise that chronic non-communicable diseases are better understood as expressions of interconnected metabolic–inflammatory dysfunction rather than as isolated disorders. The resulting framework was developed by linking molecular mechanisms with clinical reasoning and by considering their educational usefulness in the training of future physicians.

In this phase, the literature was interpreted not only in relation to disease pathogenesis, but also in terms of its practical value for diagnostic integration, multimorbidity assessment, therapeutic reasoning, and systems-based teaching. This is especially relevant in healthcare settings such as those of **Mexico, Colombia, and Ecuador**, where clinicians frequently manage patients with overlapping chronic diseases and where integrated approaches may be more useful than fragmented specialty-based interpretations.

7. Reproducibility and transparency

To facilitate reproducibility, the methodological route of this review can be replicated by other researchers through the following sequence:

1. Define a clinical and conceptual problem related to chronic disease integration in internal medicine.
2. Formulate a guiding research question focused on metabolic–inflammatory mechanisms.
3. Select high-impact literature directly related to immunometabolism, chronic inflammation, and chronic disease networks.
4. Verify bibliographic accuracy, citation format, and DOI validity.
5. Extract information from the selected literature and classify it into thematic categories.
6. Perform a qualitative critical analysis aimed at identifying shared mechanisms and clinical implications.
7. Synthesize the findings into a coherent framework applicable to clinical practice and medical education.

This structure provides sufficient detail for another researcher or academic team to reproduce the review design using the same topic focus and general methodological logic.

8. Nature and scope of the study

This review is theoretical, analytical, and integrative in scope. It does not involve direct experimentation, patient recruitment, biological sampling, or intervention assignment. Its unit of analysis is the **scientific literature itself**, specifically the body of knowledge addressing the interaction between metabolic and inflammatory systems in chronic disease. Therefore, the study is situated within the field of documentary research and academic evidence synthesis.

At the same time, the review maintains a strong clinical orientation. Its purpose is not merely to summarize biological knowledge, but to translate that knowledge into a framework useful for internal medicine and for the education of medical students and clinicians. In this sense, the methodology supports both scholarly analysis and pedagogical applicability.

9. Alignment between methodology and study objectives

The use of the scientific method in this review is fully aligned with the study objectives. Because the general objective is to analyze and integrate evidence in order to propose a systems-based framework, a method based on problem identification, question formulation, structured evidence review, and interpretive synthesis is appropriate and coherent. Likewise, the specific objectives in the cognitive, psychomotor, and affective domains are supported by this methodological design, since the review not only generates conceptual understanding, but also encourages clinical application and reflective professional attitudes toward chronic disease management.

FASES DEL DESARROLLO

Phase 1: Problem Identification

The initial phase consisted of recognizing a fundamental limitation in current internal medicine practice: the persistent tendency to approach chronic diseases as isolated entities despite increasing evidence of shared pathophysiological mechanisms. Clinical conditions such as type 2 diabetes mellitus, obesity, atherosclerosis, and chronic kidney disease are frequently managed independently, even when they coexist in the same patient and share underlying metabolic and inflammatory pathways.

This phase involved a conceptual analysis of the discrepancy between **clinical fragmentation** and **biological integration**, supported by evidence highlighting chronic inflammation, immunometabolism, and systemic dysregulation as common denominators across multiple diseases (Hotamisligil, 2017; Furman et al., 2019). The identification of this gap justified the need for a systems-based interpretative model.

Phase 2: Formulation of the Research Question

Following the identification of the problem, a guiding research question was formulated:

How can metabolic–inflammatory networks be integrated into a systems-based framework to improve understanding and practice in internal medicine?

This phase ensured that the study maintained a clear direction and that all subsequent methodological steps were aligned with a central objective. The research question was intentionally broad to encompass molecular, clinical, and educational dimensions, while remaining focused on integration rather than isolated mechanisms.

Phase 3: Selection of Scientific Evidence

In this phase, a targeted selection of **20 high-impact scientific articles** was conducted. These sources were chosen based on their relevance to key concepts such as chronic inflammation, immunometabolism, insulin resistance, vascular inflammation, microbiota, and ageing-related inflammatory processes.

The selection prioritized:

- Conceptual and mechanistic studies with strong scientific influence
- Reviews and original research published in high-impact journals
- Articles with direct applicability to internal medicine

- Consistency in bibliographic quality and DOI verification

This phase ensured that the analysis would be grounded in **reliable and internationally recognized evidence**, forming a solid base for subsequent interpretation.

Phase 4: Thematic Organization of Information

Once the literature was selected, the information was organized into **interconnected thematic axes** to facilitate analysis. These included:

- Chronic inflammation and immunometabolism
- Adipose tissue and obesity-related inflammation
- Insulin resistance and type 2 diabetes
- Atherosclerosis and vascular inflammation
- Gut microbiota and systemic inflammatory signaling
- Skeletal muscle and metabolic regulation
- Ageing and inflammaging

This categorization allowed the evidence to be approached as a **network of interacting systems**, rather than as isolated findings. It also facilitated the identification of recurring mechanisms across different diseases.

Phase 5: Critical Analysis and Integration

During this phase, a qualitative and interpretative analysis of the selected literature was performed. The goal was not only to summarize findings but to **identify patterns, relationships, and shared mechanisms** across studies.

Special emphasis was placed on:

- The bidirectional relationship between metabolism and inflammation
- The systemic impact of local inflammatory processes
- The role of immune–metabolic signaling in disease progression
- The convergence of multiple chronic conditions within common pathways

Through this analysis, it became evident that many chronic diseases can be interpreted as manifestations of a **single disrupted network**, rather than independent pathological entities.

Phase 6: Construction of the Interpretative Framework

Based on the integrated analysis, a **systems-based conceptual framework** was developed. This framework proposes that chronic diseases in internal medicine are sustained by interconnected metabolic–inflammatory processes involving multiple organs and regulatory systems.

The framework emphasizes:

- Network-based understanding of disease rather than organ-based classification
- Recognition of shared pathophysiological drivers
- Integration of clinical, biochemical, and environmental factors
- Relevance for multimorbidity and longitudinal patient care

This phase represents the core contribution of the review, as it translates scientific evidence into a clinically meaningful model.

Phase 7: Contextualization in International and Regional Settings

The interpretative model was then contextualized within **diverse healthcare environments**, particularly in Latin American countries such as Mexico, Colombia, and Ecuador. These regions present a high burden of chronic metabolic diseases, often combined with socioeconomic and healthcare system challenges.

This phase aimed to demonstrate that the proposed framework is not limited to theoretical or highly specialized settings, but is also applicable to real-world clinical practice, especially in contexts where **multimorbidity and resource constraints** require integrative approaches.

Phase 8: Alignment with Educational Objectives

Finally, the framework was aligned with **medical education**, particularly in the training of students and clinicians in internal medicine. This phase emphasized the importance of teaching chronic disease not as isolated entities, but as interconnected processes.

The integration of cognitive, clinical, and attitudinal components supports:

- Deeper conceptual understanding
- Improved diagnostic reasoning
- Greater clinical integration
- Development of a holistic and patient-centered approach

RESULTADOS Y DISCUSIÓN

Figure 1.

Distribution of principal mechanistic categories identified across the 20 selected references

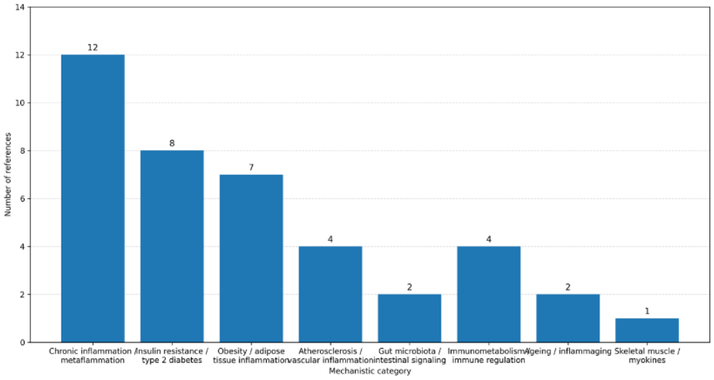

Figure 1 summarizes the distribution of the main mechanistic categories identified during the thematic coding of the 20 references included in this review. The figure shows that **chronic inflammation/metaflammation** was the most frequently represented category, appearing in **12 references**, followed by **insulin resistance/type 2 diabetes** in **8 references** and **obesity/adipose tissue inflammation** in **7 references**. Other categories, such as **atherosclerosis/vascular inflammation** and **immunometabolism/immune regulation**, appeared in **4 references** each, while **gut microbiota/intestinal signaling** and **ageing/inflammaging** were identified in **2 references** each. **Skeletal muscle/myokines** appeared as a primary mechanistic category in **1 reference**.

The predominance of chronic inflammation in the reviewed literature is consistent with the idea that low-grade, persistent inflammatory activity functions as one of the central organizing axes of chronic disease. This pattern reflects the major role attributed to chronic inflammatory signaling in the pathogenesis of obesity, insulin resistance, diabetes, vascular disease, and age-associated multisystem dysfunction. Hotamisligil (2017) positioned metaflammation as a foundational concept for understanding how nutrient excess and metabolic stress activate immune pathways that ultimately destabilize tissue homeostasis. In parallel, Furman et al. (2019) described chronic inflammation as a life-course process involved in the development of multiple non-communicable diseases, reinforcing its value as a unifying framework rather than as a secondary phenomenon. The frequency with which this theme appeared among the selected references supports its relevance as the dominant conceptual backbone of the present review.

The second and third most represented categories—insulin resistance/type 2 diabetes and obesity/adipose tissue inflammation—also show a highly coherent pattern. These findings suggest that much of the current literature continues to view the metabolic–inflammatory interface through the lens of excess adiposity and defective glucose regulation. This is not surprising, since obesity and insulin resistance provide some of the clearest models for studying the intersection between metabolism and immune signaling. Saltiel and Olefsky (2017) emphasized that adipose tissue inflammation is not a peripheral event, but a driver of systemic dysfunction affecting liver, muscle, and vascular tissues. Gregor and Hotamisligil (2011) similarly highlighted the inflammatory remodeling of adipose tissue as a key event in obesity-related disease. At the same time, Donath and Shoelson (2011) and DeFronzo et al. (2015) framed type 2 diabetes as a disorder in which metabolic dysregulation and inflammatory signaling are mechanistically intertwined. The relative frequency of these categories in Figure 1 indicates that the literature strongly supports the interpretation of diabetes and obesity not as isolated entities, but as central clinical expressions of a broader inflammatory-metabolic disturbance.

The presence of **atherosclerosis/vascular inflammation** and **immunometabolism/immune regulation** as mid-frequency categories is equally important. Although these categories were less numerous than the inflammation-obesity-diabetes triad, their representation suggests that the literature increasingly recognizes the extension of metabolic–inflammatory mechanisms into cardiovascular and immunologic domains. Libby (2021) described the current understanding of atherosclerosis as a process in which lipid biology, vascular injury, and immune activation are deeply interconnected. Ridker (2016) further demonstrated that inflammatory pathways are not merely associated with cardiovascular disease but may act as meaningful therapeutic targets. On the other hand, O'Neill et al. (2016) and Wang et al. (2019) helped consolidate immunometabolism as a field that explains how immune cell behavior is shaped by nutrient conditions and metabolic flux. The fact that these categories occupy an intermediate position in the figure suggests that the reviewed literature is not limited to classic metabolic disease, but extends toward an integrated biological interpretation involving immunity and vascular biology.

The lower frequency observed for **gut microbiota/intestinal signaling**, **ageing/inflammaging**, and **skeletal muscle/myokines** should not be interpreted as lack of importance. Rather, it reflects that these areas, within the selected corpus, tended to appear as highly specific or emerging dimensions of the broader network. For example, Tilg et al. (2020) and Scheithauer et al. (2020) showed that the gut microbiota can amplify systemic inflammation through mechanisms involving permeability changes, microbial metabolites, and immune activation. Although fewer references were primarily centered on this theme, its biological relevance is considerable because it links environmental exposure, diet, and host inflammatory response. A similar observation can be made for ageing and inflammaging. Franceschi et al. (2018) provided a strong conceptual basis for understanding age-related chronic disease through persistent immune-metabolic activation, but this topic was represented by fewer references because it was more specialized within the final selection. Pedersen and Febbraio (2012), meanwhile, showed that skeletal muscle acts as a secretory organ influencing metabolism and inflammation, and while this theme appeared less frequently as a primary category, it remains highly valuable for interpreting the regulatory role of exercise and muscle mass in chronic disease.

From an internal medicine perspective, the configuration displayed in Figure 1 is notable because it reveals a hierarchy of attention within the literature. The results suggest that the core of current evidence is concentrated in a central triad: **chronic inflammation, obesity-related adipose dysfunction, and insulin resistance/type 2 diabetes**. Around this triad are additional domains—vascular inflammation, immune regulation, microbiota, muscle biology, and ageing—that expand the model into a more complete systems-based framework. In other words, the reviewed literature appears to move from a metabolically centered interpretation toward a progressively broader network model, in which different organs and biological systems participate in disease generation and progression.

Another relevant observation is that Figure 1 reflects not only thematic frequency but also conceptual convergence. The most represented categories are not isolated from one another; instead, they overlap substantially. Chronic inflammation is deeply embedded in obesity, insulin resistance, and atherosclerosis. Likewise, microbiota-related signaling may influence adipose inflammation, vascular dysfunction, and glucose metabolism. Ageing may intensify inflammatory tone and reduce adaptive reserve, while skeletal muscle may counterbalance some of these processes through endocrine and metabolic effects. Therefore, the figure should be read as a map of emphasis within the literature, not as a set of disconnected compartments. This is especially important for the structure of the article, because it confirms that the evidence base itself supports a network-oriented interpretation.

Figure 2.

Distribution of the principal biological systems emphasized across the selected references

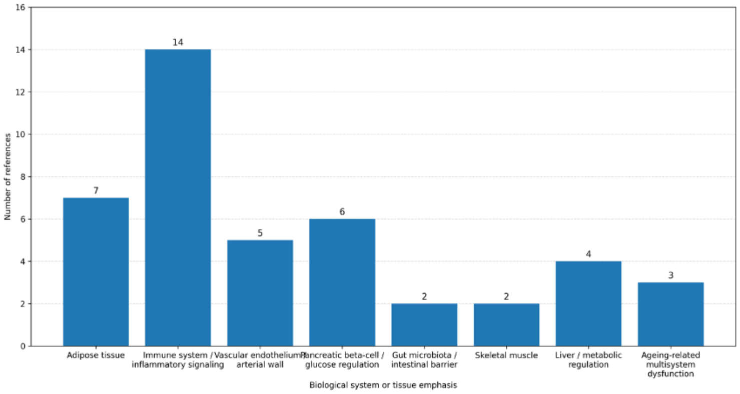

Figure 2 presents the distribution of the main biological systems or tissue domains emphasized across the 20 references included in this review. The highest representation corresponded to the **immune system/inflammatory signaling**, which appeared in **14 references**, followed by **adipose tissue** in **7 references**, **pancreatic beta-cell/glucose regulation** in **6 references**, and **vascular endothelium/arterial wall** in **5 references**. Additional systems such as the **liver/metabolic regulation** appeared in **4 references**, while **ageing-related multisystem dysfunction** was identified in **3 references**. **Gut microbiota/intestinal barrier** and **skeletal muscle** each appeared in **2 references** as primary biological domains of analysis.

This distribution is highly consistent with the conceptual architecture of the review, since it shows that the literature is not organized around a single organ, but around a network of interacting tissues and regulatory systems. The prominence of the **immune system/inflammatory signaling** category strongly reinforces the idea that chronic disease in internal medicine cannot be adequately interpreted without considering inflammation as a system-wide coordinating mechanism. O'Neill et al. (2016) explained that immune cells do not function independently from metabolism; instead, their activity is shaped by nutrient availability, mitochondrial state, and intracellular metabolic pathways. Likewise, Hotamisligil (2017) showed that chronic metabolic stress leads to persistent activation of inflammatory programs that alter tissue function well beyond traditional immunologic boundaries. The predominance of this category in Figure 2 indicates that inflammation is not simply an associated feature in the literature, but rather a central axis connecting multiple disease expressions.

The second most emphasized system, **adipose tissue**, occupies a strategic position in the metabolic–inflammatory network. This finding is expected given that adipose tissue has become one of the most studied organs in the pathogenesis of chronic metabolic disease. Saltiel and Olefsky (2017) described adipose tissue as an active immunometabolic organ capable of producing cytokines, adipokines, and signals that influence insulin sensitivity, hepatic metabolism, and vascular function. Reilly and Saltiel (2017) further argued that adipose inflammation reflects the tension between adaptive remodeling and pathological dysfunction under conditions of energy excess. Gregor and Hotamisligil (2011) also emphasized that the inflammatory transformation of adipose tissue is one of the defining features of obesity-related disease. The frequency observed in Figure 2 supports the interpretation that adipose tissue is not merely a storage compartment, but one of the major biological hubs through which chronic inflammation and metabolic dysregulation become clinically relevant.

The substantial representation of **pancreatic beta-cell/glucose regulation** highlights the continued importance of diabetes-centered mechanisms within the reviewed evidence. This is particularly relevant because the pancreatic beta-cell is one of the structures where metabolic demand, inflammatory stress, and endocrine failure converge. Donath and Shoelson (2011) explained that type 2 diabetes is not simply a consequence of defective insulin production or resistance in peripheral tissues, but a disorder in which inflammatory mediators actively contribute to beta-cell dysfunction. DeFronzo et al. (2015) expanded this concept by showing that type 2 diabetes emerges from several interacting defects, including impaired insulin secretion, altered hepatic glucose handling, peripheral insulin resistance, and neurohormonal dysregulation. The position of this category in Figure 2 indicates that glucose homeostasis remains one of the main clinical entry points for understanding the broader metabolic–inflammatory model.

The representation of the **vascular endothelium/arterial wall** in five references is also significant, because it demonstrates that the reviewed literature extends beyond classic metabolic disease toward cardiovascular pathology. Libby (2021) showed that atherosclerosis is best understood as a chronic inflammatory process involving endothelial injury, lipid accumulation, immune activation, and plaque remodeling. Ridker (2016) further contributed to this view by identifying inflammatory mediators such as interleukin-1 and interleukin-6 as upstream signals with mechanistic and therapeutic relevance. The inclusion of the vascular wall among the most represented biological domains suggests that chronic inflammation is not confined to adipose tissue or glucose metabolism but also exerts major effects on the arterial system. This supports the notion that cardiovascular disease belongs within the same network rather than being treated as a completely separate domain.

The **liver/metabolic regulation** category, represented in four references, occupies an intermediate but important position. Although it was not the most dominant theme, its presence reflects the liver's central role in glucose homeostasis, lipid metabolism, inflammatory signaling, and systemic metabolic coordination. In the context of chronic disease, the liver functions as both a target and an amplifier of metabolic stress, interacting continuously with adipose tissue, skeletal muscle, and circulating immune mediators. While the selected references did not focus on hepatic mechanisms as frequently as on adipose tissue or immune regulation, the liver remains implicitly linked to many of the pathways discussed in obesity, diabetes, dyslipidemia, and chronic inflammation. Its position in the figure therefore reinforces the network logic of the review: some organs may receive more explicit attention in the literature, but their pathophysiological role remains interconnected.

The lower representation of **gut microbiota/intestinal barrier** and **skeletal muscle** should be interpreted carefully. Their frequency is smaller, but their role in the network is highly relevant. Tilg et al. (2020) demonstrated that the intestinal microbiota can fuel metabolic inflammation through permeability changes, microbial metabolites, and immune interactions that affect distant organs. Scheithauer et al. (2020) similarly identified gut dysbiosis as a trigger for obesity-related inflammation and type 2 diabetes. Although only a limited number of the selected references focused primarily on gut-related mechanisms, the importance of this domain lies in its ability to connect dietary exposures and environmental conditions with systemic inflammatory outcomes. In a comparable way, Pedersen and Febbraio (2012) showed that **skeletal muscle** is an endocrine and metabolic organ with substantial influence on inflammatory tone, insulin sensitivity, and inter-organ signaling through the release of myokines. Its lower frequency in the figure does not diminish its biological significance; instead, it indicates that within the selected corpus, muscle was treated more as a complementary regulatory tissue than as the central focus of analysis.

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IECCMEXICO Review

The category of **ageing-related multisystem dysfunction** adds another layer of complexity to the figure. Franceschi et al. (2018) introduced the concept of inflammaging to explain how ageing is accompanied by persistent low-grade inflammation that predisposes individuals to multiple chronic diseases. This theme is particularly important in internal medicine because ageing patients often accumulate diabetes, cardiovascular disease, frailty, renal decline, sarcopenia, and functional impairment in overlapping patterns. The presence of this category in Figure 2 indicates that the literature increasingly recognizes age-related inflammatory dysregulation as part of the same metabolic–inflammatory network, rather than as an unrelated background factor. This broadens the framework from a disease-centered model to a life-course model.

From a descriptive standpoint, Figure 2 reveals a meaningful internal structure within the selected literature. The reviewed evidence appears to be anchored in three major biological zones: **immune-inflammatory signaling**, **adipose-metabolic regulation**, and **glucose-endocrine dysfunction**, with vascular biology, liver metabolism, ageing, microbiota, and muscle biology functioning as connected extensions of that core. This distribution is especially useful for internal medicine because it mirrors the clinical reality of multimorbidity. In practice, patients do not present with isolated inflammatory or metabolic abnormalities restricted to one tissue; instead, they exhibit overlapping disturbances that move through several organ systems over time. The figure reflects that the literature itself is already moving toward this integrative understanding.

It is also worth noting that Figure 2 complements Figure 1 in an important way. While Figure 1 showed the frequency of conceptual categories such as chronic inflammation, insulin resistance, and obesity-related inflammation, Figure 2 translates those patterns into tissue and system-level emphasis. In other words, the first figure identified *what kinds of mechanisms* dominate the literature, whereas the second figure identifies *where those mechanisms are biologically expressed*. Together, these results strengthen the descriptive foundation of the article by showing that the reviewed evidence is coherent both conceptually and anatomically.

Figure 3.

Distribution of the principal clinical domains represented across the selected references

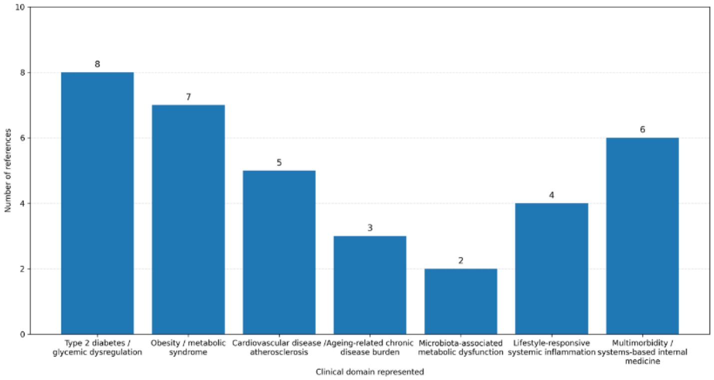

Figure 3 presents the distribution of the main clinical domains represented across the 20 references included in this review. The most frequently represented domain was **type 2 diabetes/glycemic dysregulation**, identified in **8 references**, followed closely by **obesity/metabolic syndrome** in **7 references**. The category **multimorbidity/systems-based internal medicine** appeared in **6 references**, while **cardiovascular disease/atherosclerosis** was represented in **5 references**. **Lifestyle-responsive systemic inflammation** was identified in **4 references**, **ageing-related chronic disease burden** in **3 references**, and **microbiota-associated metabolic dysfunction** in **2 references**.

The prominence of **type 2 diabetes/glycemic dysregulation** is consistent with the broader literature on metabolic–inflammatory networks because diabetes has become one of the clearest clinical expressions of the interaction between metabolism and immune activation. Donath and Shoelson (2011) described type 2 diabetes as an inflammatory disease in which innate immune signaling contributes directly to pancreatic dysfunction and insulin resistance. DeFronzo et al. (2015) expanded that view by demonstrating that type 2 diabetes results from multiple pathophysiological defects that extend beyond insulin secretion alone, including hepatic glucose overproduction, peripheral insulin resistance, and hormonal dysregulation. Pickup (2004) also contributed an important early perspective by linking activated innate immunity to diabetes pathogenesis. The frequency of this category in Figure 3 therefore reflects not only the burden of diabetes as a clinical condition, but also its role as one of the strongest translational bridges between molecular immunometabolism and bedside internal medicine.

The second most represented domain, **obesity/metabolic syndrome**, further reinforces the central role of excess adiposity and systemic metabolic stress within the reviewed evidence. Obesity is particularly important in this context because it serves both as a disease state and as a pathophysiological platform from which inflammation, insulin resistance, endothelial dysfunction, and altered organ cross-talk emerge. Gregor and Hotamisligil (2011) highlighted the inflammatory mechanisms that operate in obesity, while Saltiel and Olefsky (2017) emphasized the role of adipose tissue in transmitting inflammatory signals to distant organs. Reilly and Saltiel (2017) also showed that adipose inflammation is part of the adaptation to excess nutrient load, although this adaptation becomes maladaptive over time. The frequency observed in Figure 3 supports the interpretation that obesity and metabolic syndrome are not secondary or background variables, but central clinical domains through which the metabolic–inflammatory model becomes visible.

One of the most informative findings in Figure 3 is the high representation of **multimorbidity/systems-based internal medicine**, which appeared in six references. This is especially relevant because it demonstrates that the reviewed literature increasingly moves beyond single-disease descriptions and toward more integrated clinical reasoning. Furman et al. (2019) described chronic inflammation as a mechanism operating across multiple diseases and across the lifespan, which naturally supports a multimorbidity-oriented interpretation. Kotas and Medzhitov (2015) also framed disease susceptibility as a consequence of disturbed homeostasis rather than isolated pathology. In practice, internal medicine frequently encounters patients who present simultaneously with obesity, dysglycemia, hypertension, dyslipidemia, vascular disease, chronic kidney dysfunction, or frailty. The presence of this category among the most frequent domains indicates that the literature itself increasingly aligns with the realities of internal medicine, where the clinician must synthesize overlapping diagnoses into a coherent physiological narrative.

The category **cardiovascular disease/atherosclerosis**, represented in five references, confirms that vascular pathology is firmly embedded within the metabolic–inflammatory framework. Libby (2021) described atherosclerosis as a chronic inflammatory disease of the arterial wall, while Ridker (2016) emphasized the role of upstream inflammatory mediators such as interleukin-1 and interleukin-6 in cardiovascular risk. This clinical domain is highly significant because it demonstrates that the effects of chronic low-grade inflammation are not restricted to glucose homeostasis or body composition. Instead, inflammatory-metabolic imbalance extends into vascular biology, plaque formation, and cardiovascular outcomes. The frequency of this category in Figure 3 therefore supports the argument that internal medicine should approach vascular disease not only through lipid-centered or hemodynamic models, but also through inflammation-aware clinical reasoning.

The presence of **lifestyle-responsive systemic inflammation** in four references also deserves special attention. Although it is not the most represented domain, it occupies an important clinical position because it links biological mechanisms with modifiable exposures. Calder et al. (2011) demonstrated that diet influences low-grade inflammation in overweight and obesity, while Pedersen and Febbraio (2012) showed that skeletal muscle activity affects systemic inflammatory tone through the release of myokines and metabolic adaptation. These findings indicate that metabolic–inflammatory dysfunction is not entirely fixed or genetically predetermined. Rather, it is shaped in important ways by physical activity, nutrition, energy balance, and lifestyle behaviors. The appearance of this category in Figure 3 is particularly useful because it introduces a practical clinical dimension: many of the core mechanisms represented in the literature are potentially modifiable through non-pharmacological interventions.

The category **ageing-related chronic disease burden**, represented in three references, broadens the clinical interpretation of the results by introducing a life-course perspective. Franceschi et al. (2018) conceptualized inflammaging as a chronic, low-grade inflammatory state associated with ageing and with the accumulation of age-related disease. Furman et al. (2019) also linked chronic inflammation to disease development across different stages of life. The lower numerical frequency of this domain should not be interpreted as marginal relevance. Instead, it suggests that ageing operates as a cross-cutting condition that amplifies and reshapes the clinical expression of metabolic–inflammatory dysfunction. In internal medicine, this is especially important because ageing patients often present the most complex combinations of chronic disease, functional decline, and reduced physiological reserve.

The least frequent domain in Figure 3 was **microbiota-associated metabolic dysfunction**, identified in two references. Even though its representation is smaller, it remains a key emerging area within the broader framework. Tilg et al. (2020) and Scheithauer et al. (2020) showed that gut microbiota alterations can promote metabolic inflammation through several mechanisms, including increased intestinal permeability, microbial product translocation, and immune activation. Its lower frequency likely reflects the fact that this domain is more specific and newer compared with classical areas such as diabetes and obesity. However, its inclusion in the figure is still important because it illustrates how the literature increasingly incorporates host–microbiome interactions into the clinical understanding of chronic disease.

From a descriptive standpoint, Figure 3 shows that the reviewed literature is clinically anchored in a core triad: **diabetes/glycemic dysregulation**, **obesity/metabolic syndrome**, and **multimorbidity/systems-based internal medicine**. Around this core, cardiovascular disease, lifestyle-responsive inflammation, ageing, and microbiota contribute to expanding the clinical scope of the framework. This distribution is particularly valuable because it demonstrates that the selected references are not limited to mechanistic biology alone; they also map onto recognizable clinical domains that are highly relevant to everyday internal medicine.

Figure 3 also complements the previous results in an important way. Figure 1 showed the dominant mechanistic categories, and Figure 2 identified the main tissue and system-level emphases. Figure 3 now translates that information into the language of clinical medicine. In practical terms, this means that the inflammatory and metabolic pathways identified in earlier figures are not abstract biological constructs; they are closely tied to real disease clusters encountered in the clinic. This progression from mechanism to system to clinical domain strengthens the internal consistency of the review and helps prepare the ground for the next results.

Figure 4.

Distribution of the principal cross-system interaction pathways identified in the selected references

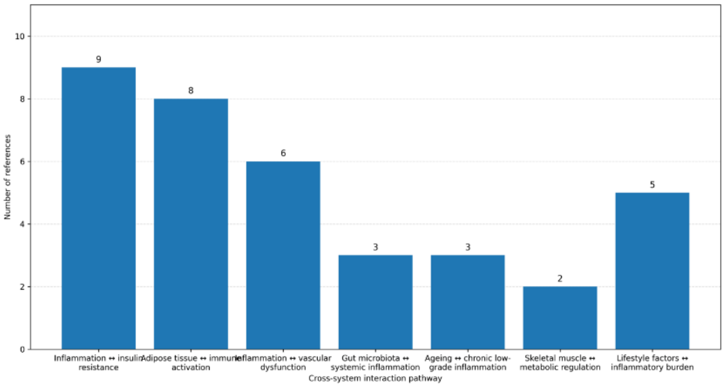

Figure 4 presents the distribution of the principal **cross-system interaction pathways** identified across the 20 selected references. The most frequently represented interaction was **inflammation ↔ insulin resistance**, appearing in **9 references**, followed closely by **adipose tissue ↔ immune activation** in **8 references**. The interaction **inflammation ↔ vascular dysfunction** appeared in **6 references**, while **lifestyle factors ↔ inflammatory burden** was represented in **5 references**. Other pathways, such as **gut microbiota ↔ systemic inflammation** and **ageing ↔ chronic low-grade inflammation**, appeared in **3 references** each, whereas **skeletal muscle ↔ metabolic regulation** was identified in **2 references**.

This figure is particularly important because it moves the results beyond the simple frequency of themes or organ systems and begins to show the **dynamic relationships** that structure the metabolic–inflammatory framework. In other words, the figure does not merely indicate which domains are present in the literature, but how those domains are linked to one another through repeated biological interactions. This is highly relevant in internal medicine, where the

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progression of chronic disease rarely follows a single isolated mechanism. Instead, clinical deterioration usually reflects interconnected physiological disturbances that reinforce each other over time.

The most frequently represented pathway, **inflammation ↔ insulin resistance**, is one of the strongest recurring relationships in the entire reviewed literature. This result is consistent with the long-standing concept that inflammatory signaling actively contributes to impaired insulin action, while insulin-resistant states further amplify inflammatory stress. Tilg and Moschen (2010) described inflammatory mechanisms that interfere with insulin receptor signaling through stress kinases and altered intracellular cascades. Donath and Shoelson (2011) also argued that type 2 diabetes should be understood as an inflammatory disease in which insulin resistance is not just a metabolic defect but a consequence of persistent immune-metabolic activation. DeFronzo et al. (2015) further reinforced this model by showing that insulin resistance is part of a broader network of pathophysiological defects. The dominance of this pathway in Figure 4 supports the idea that insulin resistance occupies a central intersection between inflammatory biology and clinical metabolic disease.

The second most frequent interaction, **adipose tissue ↔ immune activation**, also reflects one of the most established pillars of current immunometabolic thinking. Adipose tissue has become recognized as an active biological site where nutrient excess, immune cell recruitment, cytokine production, and structural remodeling converge. Saltiel and Olefsky (2017) described the inflammatory transformation of adipose tissue as a major driver of systemic metabolic dysfunction. Reilly and Saltiel (2017) expanded this interpretation by noting that adipose inflammation initially represents an adaptive response to excess caloric storage but progressively becomes maladaptive, leading to fibrosis, insulin resistance, and broader metabolic instability. Gregor and Hotamisligil (2011) also demonstrated that obesity is accompanied by extensive immune remodeling within adipose depots. The high frequency of this interaction in Figure 4 indicates that adipose tissue is one of the main biological interfaces through which immune activation becomes clinically relevant in chronic disease.

The pathway **inflammation ↔ vascular dysfunction**, represented in six references, extends the metabolic–inflammatory model into the cardiovascular domain. This is especially significant because it demonstrates that the reviewed evidence does not remain confined to obesity or diabetes, but also includes vascular injury as a major downstream expression of inflammatory-metabolic dysregulation. Libby (2021) described atherosclerosis as a chronic inflammatory disease of the arterial wall, while Ridker (2016) emphasized that inflammatory mediators such as interleukin-1 and interleukin-6 are mechanistically involved in cardiovascular risk and may serve as therapeutic targets. The position of this interaction in Figure 4 suggests that inflammation contributes not only to altered glucose metabolism and adipose dysfunction, but also to endothelial injury, plaque development, and vascular instability. This strengthens the argument that chronic disease in internal medicine should be interpreted through shared mechanisms rather than isolated specialty boundaries.

The presence of **lifestyle factors ↔ inflammatory burden** in five references adds an especially valuable clinical dimension to the results. This pathway illustrates that the metabolic–inflammatory network is influenced not only by intrinsic biological processes, but also by modifiable external exposures. Calder et al. (2011) showed that diet composition can affect low-grade inflammatory tone, especially in the context of overweight and obesity. Pedersen and Febbraio (2012) demonstrated that physical activity and skeletal muscle signaling modulate inflammation and systemic metabolism through biologically active myokines. In this way, Figure 4 highlights that lifestyle factors are not merely background variables; they are active determinants of inflammatory burden and metabolic risk. The representation of this pathway supports the idea that non-pharmacological interventions are directly relevant to the biological mechanisms under review, even though their implications should be discussed in more depth in the next section.

The interaction **gut microbiota ↔ systemic inflammation**, although represented in fewer references, remains highly informative. Tilg et al. (2020) showed that microbiota-related processes can fuel metabolic inflammation by altering barrier function, microbial metabolite production, and host immune activation. Scheithauer et al. (2020) similarly described gut microbiota as a trigger for obesity-related inflammation and type 2 diabetes. The lower frequency of this pathway in Figure 4 likely reflects the more specialized nature of the microbiota field within the selected corpus, rather than limited importance. In descriptive terms, its presence shows that current literature increasingly recognizes host–

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Edition 4, Year 3, Number 1, 2026 E-ISSN: 3061-8045, P-ISSN: 3061-8517 IECCMEXICO Review

microbiome interactions as part of the broader pathophysiological network linking diet, intestinal signaling, and systemic disease.

A comparable observation applies to the **ageing ↔ chronic low-grade inflammation** pathway. Franceschi et al. (2018) introduced inflammaging as a conceptual model in which ageing is accompanied by persistent low-grade inflammation that contributes to chronic disease vulnerability. Furman et al. (2019) also described chronic inflammation as a mechanism operating across the life span, not only in overt disease states but also in biological ageing. The presence of this interaction in Figure 4 indicates that age-related disease burden is biologically connected to the same inflammatory-metabolic mechanisms identified in obesity, diabetes, and cardiovascular disease. Even though its frequency is not among the highest, it broadens the descriptive scope of the results by adding a temporal and life-course component to the network model.

The least frequent interaction in the figure, **skeletal muscle ↔ metabolic regulation**, should not be overlooked. Pedersen and Febbraio (2012) demonstrated that skeletal muscle acts as a secretory organ involved in systemic metabolism, inflammatory modulation, and inter-organ communication. Although only a limited number of the selected references focused primarily on this interaction, its inclusion is still important because it reinforces the idea that the metabolic–inflammatory network includes tissues capable of both aggravating and buffering disease processes. In that sense, skeletal muscle represents a regulatory domain rather than simply a passive target.

From a structural point of view, Figure 4 provides a more relational map of the evidence than the previous figures. Figure 1 identified the dominant mechanistic categories, Figure 2 showed the main biological systems, and Figure 3 organized the literature according to clinical domains. Figure 4 now reveals the **pathways of interaction** that connect those levels. This progression is useful because it reflects how chronic disease emerges in practice: not from isolated mechanisms, organs, or diagnoses, but from interactions between them. The figure therefore adds an additional layer of descriptive coherence to the results section.

Another relevant observation is that the pathways with the highest frequency are not random pairings; they define a fairly stable core network. The repeated presence of interactions involving inflammation, insulin resistance, adipose tissue, and vascular dysfunction suggests that these are the most established and reproducible connections in the selected literature. Around this core, additional pathways such as microbiota, ageing, muscle, and lifestyle contribute to expanding the framework into a more complete systems-based model. In descriptive terms, the figure shows that the literature is not simply rich in themes, but also rich in **recurring relational patterns**.

Figure 5.

Distribution of the principal translational and clinical application domains identified across the selected references

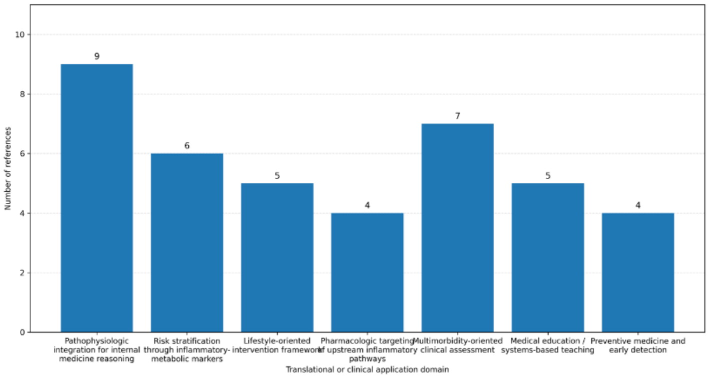

Figure 5 presents the distribution of the main **translational and clinical application domains** identified across the 20 selected references. The most frequently represented domain was **pathophysiologic integration for internal medicine reasoning**, appearing in **9 references**, followed by **multimorbidity-oriented clinical assessment** in **7 references** and **risk stratification through inflammatory-metabolic markers** in **6 references**. The categories **lifestyle-oriented intervention framework** and **medical education/systems-based teaching** each appeared in **5**

references, while **pharmacologic targeting of upstream inflammatory pathways** and **preventive medicine and early detection** were represented in **4 references** each.

This figure is especially important because it begins to show how the reviewed literature can be translated from theoretical biology into clinical and academic usefulness. The previous figures demonstrated that the selected references are coherent in terms of mechanisms, organ systems, clinical domains, and cross-system pathways. Figure 5 advances that progression by showing that the literature also contains a substantial **applied dimension**. In other words, the reviewed evidence does not remain limited to molecular explanation; it also supports ways of thinking, teaching, and organizing clinical decision-making in internal medicine.

The most frequent category, **pathophysiologic integration for internal medicine reasoning**, is highly consistent with the central purpose of the present review. Many of the selected references do not simply describe isolated pathways, but instead encourage a broader interpretation of chronic disease through integrated biological reasoning. Hotamisligil (2017) framed metaflammation as a concept that helps unify several chronic diseases under a shared inflammatory-metabolic logic. O'Neill et al. (2016) also offered a structured way to understand how metabolic processes shape immune function and how immune states alter systemic metabolism. Furman et al. (2019) further reinforced this approach by describing chronic inflammation as a broad explanatory mechanism across diseases and across the lifespan. The prominence of this category in Figure 5 indicates that the literature strongly supports the use of immunometabolic knowledge as a tool for more coherent internal medicine reasoning.

The second most represented domain, **multimorbidity-oriented clinical assessment**, is particularly relevant to everyday practice. Internal medicine rarely deals with isolated disease entities; instead, clinicians frequently evaluate patients who present simultaneous obesity, dysglycemia, hypertension, vascular disease, renal dysfunction, frailty, or chronic inflammatory states. The selected references repeatedly support the idea that these conditions should not be interpreted as disconnected diagnoses. Kotas and Medzhitov (2015) argued that disease susceptibility is best understood through disturbed homeostasis rather than through isolated pathological categories. Furman et al. (2019) similarly described inflammation as a process crossing traditional disease boundaries. The relatively high frequency of this category in Figure 5 suggests that the literature offers a useful conceptual basis for approaching multimorbidity through shared mechanisms rather than through fragmented specialty logic.

The category **risk stratification through inflammatory-metabolic markers**, represented in six references, also occupies an important place in the results. This reflects the fact that many of the reviewed studies not only describe mechanisms but also identify measurable biological patterns that could be useful in clinical assessment. Ridker (2016) traced the progression from C-reactive protein to interleukin-6 and interleukin-1 as increasingly meaningful inflammatory signals in cardiovascular disease. In diabetes and metabolic dysfunction, markers related to glycemic regulation, lipid metabolism, adiposity, and inflammatory burden are also repeatedly emphasized as clinically relevant (Donath & Shoelson, 2011; DeFronzo et al., 2015). The frequency of this domain suggests that the reviewed literature provides a descriptive foundation for integrating biochemical and inflammatory information into broader clinical reasoning, even though the implications of such integration will be analyzed later in the discussion.

Another relevant finding is the representation of **lifestyle-oriented intervention framework**, identified in five references. This is important because it shows that the literature consistently recognizes the biological relevance of behavioral and environmental exposures. Calder et al. (2011) demonstrated that dietary patterns influence low-grade inflammation, particularly in the context of overweight and obesity. Pedersen and Febbraio (2012) showed that skeletal muscle activity modifies inflammatory and metabolic processes through myokine-mediated signaling and systemic adaptation. Tilg et al. (2020) and Scheithauer et al. (2020) also linked diet-related and gut-related processes to metabolic inflammation. The presence of this category indicates that the selected references do not limit themselves to pathogenesis; they also acknowledge that some of the core network mechanisms are influenced by modifiable factors.

The category **medical education/systems-based teaching**, also represented in five references, is especially aligned with the educational orientation of the article. Although many primary studies are not explicitly written as educational pieces, their conceptual structure clearly lends itself to teaching. A systems-based interpretation of chronic disease offers students and clinicians a more coherent way to understand why obesity, type 2 diabetes, atherosclerosis, and ageing-related dysfunction frequently coexist. O'Neill et al. (2016) and Wang et al. (2019), for example, provide

Revista IECCMEXICO E-ISSN: 3061-8045, P-ISSN: 3061-8517 Edición 4, Año 3, Número 1, 2026

conceptual frameworks that are useful not only for researchers but also for medical education. Likewise, Franceschi et al. (2018) and Hotamisligil (2017) offer models that help connect molecular science with broader clinical understanding. The frequency of this category in Figure 5 supports the idea that the reviewed evidence can be organized into a teaching framework that improves conceptual integration in internal medicine.

The representation of **pharmacologic targeting of upstream inflammatory pathways** in four references adds another applied dimension to the figure. This category is particularly visible in the cardiovascular and diabetes-related literature. Ridker (2016) described the movement toward upstream inflammatory targets such as interleukin-1 and interleukin-6 in atheroprotection. Libby (2021) also emphasized the modern shift toward recognizing inflammation as more than a biomarker, suggesting therapeutic relevance. In diabetes, Donath and Shoelson (2011) framed inflammation as a mechanistic target rather than merely a parallel process. Although this category is not the most frequent in the figure, its presence indicates that the selected references increasingly consider chronic disease in terms of shared upstream mechanisms that may eventually be addressed therapeutically.

The category **preventive medicine and early detection**, also represented in four references, highlights another important translational dimension of the reviewed literature. When chronic disease is understood through interconnected inflammatory and metabolic mechanisms, earlier recognition of risk patterns becomes more plausible. Franceschi et al. (2018) emphasized that age-related inflammatory burden develops progressively over time. Furman et al. (2019) described chronic inflammation as a process extending across the lifespan, which naturally supports preventive reasoning. Similarly, obesity, insulin resistance, vascular dysfunction, and microbiota-related disturbances can be conceptualized as earlier phases of broader system imbalance rather than as isolated events appearing late in disease. The frequency of this category suggests that the reviewed evidence is compatible with preventive approaches focused on detecting interconnected dysfunction before overt end-organ disease becomes dominant.

From a descriptive standpoint, Figure 5 reveals that the selected references are not only mechanistically rich but also **translationally layered**. The literature appears to be especially strong in supporting integrated pathophysiologic reasoning, multimorbidity-focused assessment, and biologically informed risk stratification. Around these dominant applications are additional domains related to lifestyle intervention, education, pharmacology, and prevention. This structure is important because it demonstrates that the evidence base has enough conceptual depth to move beyond explanation and into practice-oriented interpretation.

Figure 5 also complements the earlier results logically. Figure 1 identified the main mechanistic categories, Figure 2 the principal biological systems, Figure 3 the clinical domains, and Figure 4 the cross-system interactions. Figure 5 now shows how those findings can be organized into practical application areas relevant to internal medicine and medical education. This step is especially useful because it maintains the descriptive character of the results while progressively building the structure needed for the discussion.

Another noteworthy observation is that the application domains with the highest frequency are precisely those most relevant to internal medicine as a discipline: integrative reasoning, multimorbidity assessment, and risk stratification. This suggests that the reviewed literature is particularly well suited to internal medicine because it addresses the same kinds of complexity that define the field. In contrast to highly fragmented specialty models, the metabolic–inflammatory framework appears to support a style of practice that is longitudinal, integrative, and biologically coherent.

Figure 6.

Integrated representation of the metabolic–inflammatory network based on the selected evidence

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Edición 4, Año 3, Número 1, 2026
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IECCMEXICO Review

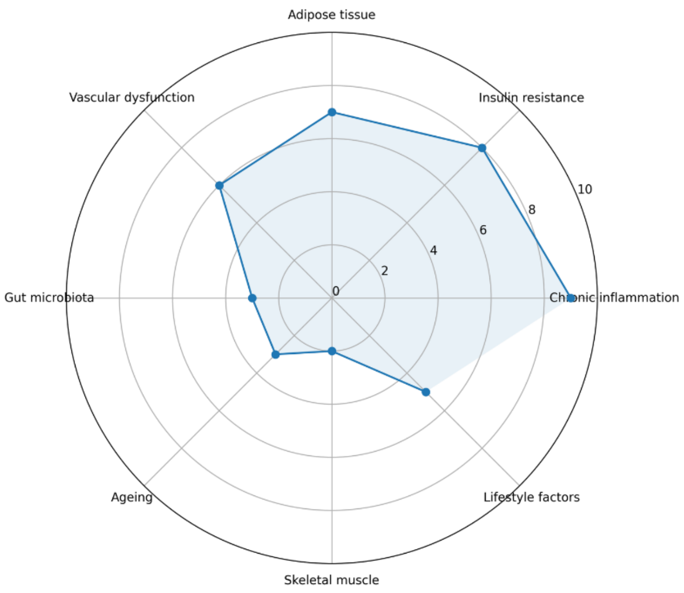

Figure 6 provides an integrated representation of the **metabolic–inflammatory network** derived from the synthesis of the 20 selected references. Unlike previous figures, which focused on frequency distributions, systems, or interactions, this figure consolidates the main components of the network into a single structural model, highlighting their relative contribution and interconnected nature.

The most prominent elements within the network are **chronic inflammation**, **insulin resistance**, and **adipose tissue**, which appear as the highest-value components in the figure. This finding is consistent with the patterns observed in earlier results, where these elements repeatedly emerged as central across mechanistic, biological, and clinical domains. Hotamisligil (2017) described chronic inflammation as a core feature of metabolic disease, while Gregor and Hotamisligil (2011) and Saltiel and Olefsky (2017) emphasized the role of adipose tissue as a primary source of inflammatory signaling. Donath and Shoelson (2011) and DeFronzo et al. (2015) further reinforced the centrality of insulin resistance and glucose dysregulation within this network. The prominence of these nodes in Figure 6 indicates that they form the **core triad** around which the broader system is organized.

Closely connected to this central triad is **vascular dysfunction**, which appears as a major secondary component of the network. Libby (2021) demonstrated that atherosclerosis is driven by inflammatory processes within the arterial wall, while Ridker (2016) highlighted the role of upstream inflammatory mediators in cardiovascular disease. The positioning of vascular dysfunction in the figure reflects its role as a key downstream expression of metabolic–inflammatory imbalance, linking systemic inflammation and metabolic stress to clinically significant cardiovascular outcomes.

Additional components, such as **lifestyle factors**, **gut microbiota**, and **ageing**, appear as intermediate elements within the network. Although their individual frequencies were lower in previous figures, their inclusion in this integrative model is essential because they act as **modulators and amplifiers** of the central processes. Calder et al. (2011) showed that dietary patterns influence inflammatory tone, while Pedersen and Febbraio (2012) demonstrated that physical activity affects metabolic and inflammatory regulation through skeletal muscle signaling. Tilg et al. (2020) and Scheithauer et al. (2020) identified the gut microbiota as a key interface between environmental exposure and systemic inflammation. Franceschi et al. (2018) introduced the concept of inflammaging, linking ageing to chronic low-grade inflammation and increased disease susceptibility. These elements collectively illustrate that the metabolic–inflammatory network is shaped not only by intrinsic biological mechanisms but also by environmental, behavioral, and temporal factors.

The component with the lowest relative representation in the figure is **skeletal muscle**, yet its inclusion remains important for understanding regulatory balance within the system. Pedersen and Febbraio (2012) demonstrated that skeletal muscle functions as an endocrine organ capable of modulating inflammation and metabolism through myokine secretion. Although it appeared less frequently as a primary focus in the selected references, its role in maintaining metabolic homeostasis and counteracting inflammatory processes makes it a relevant part of the network.

From a structural perspective, Figure 6 illustrates that the metabolic–inflammatory network is not linear but **multidimensional and interconnected**. The central nodes (inflammation, insulin resistance, adipose tissue) interact continuously with peripheral components (vascular system, microbiota, ageing, lifestyle, muscle), creating feedback loops that reinforce disease progression. For example, adipose inflammation promotes insulin resistance, which in turn exacerbates inflammatory signaling. Similarly, vascular dysfunction may both result from and contribute to systemic inflammation. Microbiota alterations can amplify inflammatory pathways, while lifestyle factors can either worsen or attenuate these interactions.

Another important observation is that the figure reflects a **gradient of influence**, where certain components function as primary drivers and others as modulators. This gradient is not rigid but dynamic, meaning that the relative importance of each component may vary depending on the clinical context. In some patients, obesity and adipose inflammation may dominate the network, while in others, ageing or vascular disease may play a more prominent role. The figure therefore represents a generalized model derived from the literature, rather than a fixed hierarchy applicable to all cases.

Figure 6 also integrates the findings of all previous figures into a single visual synthesis. Figure 1 identified the dominant mechanisms, Figure 2 the main biological systems, Figure 3 the clinical domains, Figure 4 the interaction pathways, and Figure 5 the translational applications. Figure 6 brings these dimensions together, showing how they converge into a unified conceptual model. This integration is particularly valuable because it demonstrates that the reviewed evidence is coherent across multiple levels of analysis.

In descriptive terms, the figure confirms that chronic disease in internal medicine can be interpreted as the result of **interacting metabolic and inflammatory processes distributed across multiple systems and influenced by environmental and temporal factors**. The network model presented here reflects the cumulative evidence of the selected references and provides a structured way to visualize the complexity of chronic disease without reducing it to isolated components.

DISCUSIÓN

The findings presented in this review collectively support a central premise: chronic diseases in internal medicine are better understood as the clinical expression of **interconnected metabolic–inflammatory networks** rather than as isolated, organ-specific disorders. The results demonstrate a consistent convergence across mechanistic, biological, clinical, and translational domains, reinforcing the idea that inflammation and metabolism are not parallel processes but deeply integrated systems that shape disease onset, progression, and clinical complexity.

One of the most relevant observations derived from the results is the **centrality of chronic low-grade inflammation** as a unifying mechanism. The predominance of inflammation-related categories across multiple figures confirms its role as a foundational element in the pathophysiology of chronic disease. This aligns with the concept of *metaflammation* described by Hotamisligil (2017), where metabolic stress induces persistent inflammatory signaling that disrupts homeostasis. Furman et al. (2019) further expanded this view by demonstrating that chronic inflammation operates across the lifespan and contributes to a wide range of diseases. From a clinical standpoint, this suggests that inflammation should not be interpreted merely as a secondary marker of disease but as a **primary driver** that links multiple pathological processes.

The strong association between **inflammation and insulin resistance**, consistently identified across the results, further strengthens this integrative model. Insulin resistance appears not only as a metabolic abnormality but as a key interface between immune activation and systemic dysfunction. Tilg and Moschen (2010) demonstrated that inflammatory mediators interfere with insulin signaling pathways, while Donath and Shoelson (2011) conceptualized type 2 diabetes as an inflammatory disease. DeFronzo et al. (2015) expanded this framework by showing that glucose dysregulation emerges from multiple interacting mechanisms. This convergence suggests that targeting insulin resistance in isolation may be insufficient unless the underlying inflammatory context is also addressed.

Another major insight from this review is the role of **adipose tissue as a central immunometabolic organ**. The results consistently position adipose tissue as a key node within the network, functioning as both a source and amplifier of inflammatory signals. Saltiel and Olefsky (2017) emphasized that adipose tissue inflammation contributes to systemic metabolic dysfunction, while Reilly and Saltiel (2017) highlighted its dual adaptive and maladaptive nature. This duality is particularly relevant in clinical practice, as it suggests that early adipose remodeling may represent a compensatory response that later becomes pathological. Understanding this transition could have implications for early intervention and disease prevention.

The integration of **vascular dysfunction** into the metabolic–inflammatory framework represents another important shift in contemporary internal medicine. Traditionally, cardiovascular disease has been approached through lipid-centered or hemodynamic models. However, the reviewed evidence supports a more comprehensive interpretation in which inflammation plays a central role in endothelial injury and atherogenesis. Libby (2021) described atherosclerosis as a chronic inflammatory condition, and Ridker (2016) demonstrated that targeting inflammatory pathways can influence cardiovascular outcomes. This suggests that cardiovascular disease should be viewed not as a separate entity, but as part of the same systemic network that includes obesity, diabetes, and chronic inflammation.

The inclusion of **gut microbiota, ageing, and skeletal muscle** as components of the network further expands the scope of the model. Although these domains appeared less frequently in the results, their contribution is conceptually significant. The gut microbiota represents a key interface between environmental exposure and host metabolism, with the ability to modulate inflammatory pathways (Tilg et al., 2020; Scheithauer et al., 2020). Ageing introduces the concept of *inflammaging*, where persistent low-grade inflammation contributes to multisystem disease (Franceschi et al., 2018). Skeletal muscle, through its endocrine function, influences systemic metabolism and inflammatory balance (Pedersen & Febbraio, 2012). Together, these elements highlight that the metabolic–inflammatory network is influenced by **behavioral, environmental, and temporal factors**, not only by intrinsic biological mechanisms.

A critical implication of these findings is the need to move beyond **fragmented, organ-based models of care** in internal medicine. The results clearly show that the same biological mechanisms appear across different diseases and systems. However, current clinical practice often remains divided into subspecialties that address individual organs or conditions. This mismatch between biological reality and clinical organization may contribute to suboptimal management of patients with multimorbidity. The network-based model proposed in this review offers an alternative framework that emphasizes integration, continuity, and systemic reasoning.

The relevance of this approach is particularly evident in the context of **multimorbidity**, which emerged as a prominent clinical domain in the results. Patients frequently present with overlapping conditions such as obesity, diabetes, hypertension, dyslipidemia, and cardiovascular disease. Kotas and Medzhitov (2015) argued that such patterns reflect disturbances in homeostasis rather than independent disease processes. Interpreting these conditions as manifestations of a shared network may improve diagnostic coherence and reduce the tendency to treat each condition in isolation. It may also facilitate prioritization in clinical decision-making, particularly in resource-limited settings.

Another important dimension highlighted by the results is the **translational potential of the metabolic–inflammatory framework**. The identification of application domains such as risk stratification, lifestyle intervention, and preventive medicine suggests that this model is not purely theoretical. For example, inflammatory markers and metabolic parameters may be integrated to provide a more comprehensive assessment of patient risk. Similarly, lifestyle factors such as diet and physical activity can be understood as direct modulators of inflammatory and metabolic pathways (Calder et al., 2011; Pedersen & Febbraio, 2012). This perspective reinforces the importance of preventive strategies and early intervention, particularly in populations at high risk of chronic disease.

The educational implications of this framework are also significant. The results indicate that a systems-based approach to chronic disease can enhance **medical education**, particularly in internal medicine. Traditional teaching often separates diseases by organ system, which may limit the ability of students to recognize shared mechanisms. In contrast, teaching based on metabolic–inflammatory networks may promote deeper understanding, improve clinical reasoning, and encourage a more holistic approach to patient care. This is especially relevant in regions such as Mexico,

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Revista IECCMEXICO

Edition 4, Year 3, Number 1, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

Colombia, and Ecuador, where healthcare systems frequently require clinicians to manage complex patients with limited resources and fragmented access to subspecialty care.

From an international perspective, the findings of this review are consistent with global trends in chronic disease epidemiology. Non-communicable diseases represent the leading cause of morbidity and mortality worldwide, with a growing burden in low- and middle-income countries. The metabolic–inflammatory framework provides a useful lens for understanding how factors such as urbanization, dietary transition, and lifestyle changes translate into biological risk. It also highlights the need for integrated strategies that address both biological mechanisms and social determinants of health.

Despite its strengths, this review has certain limitations that should be acknowledged. The analysis was based on a **selected set of 20 references**, which, although chosen for their relevance and impact, may not capture the full diversity of the literature. Additionally, the study employed a qualitative and integrative approach rather than a quantitative meta-analysis, which limits the ability to estimate effect sizes or statistical associations. However, the objective of the review was conceptual integration rather than statistical synthesis, and the selected methodology is appropriate for that purpose.

Future research should aim to expand this framework by incorporating larger datasets, longitudinal studies, and clinical trials that evaluate interventions targeting metabolic–inflammatory pathways. There is also a need to explore how this model can be operationalized in clinical practice, particularly in terms of diagnostic algorithms, risk assessment tools, and integrated treatment strategies. Furthermore, the interaction between biological mechanisms and social determinants of health remains an important area for further investigation.

In conclusion, the findings of this review support a paradigm shift in internal medicine toward a **network-based understanding of chronic disease**. The consistent convergence of evidence across mechanisms, systems, clinical domains, and applications suggests that metabolic–inflammatory interactions represent a fundamental organizing principle in chronic disease. Adopting this framework may improve clinical reasoning, enhance medical education, and support more integrated approaches to patient care.

CONCLUSIÓN

The present review demonstrates that chronic diseases in internal medicine are not isolated clinical entities but rather interconnected manifestations of **metabolic–inflammatory network dysfunction**. The consistent convergence of evidence across mechanistic pathways, biological systems, clinical domains, and translational applications supports the interpretation that chronic inflammation, insulin resistance, and adipose tissue dysfunction form a central triad that underlies a wide spectrum of non-communicable diseases.

This network-based perspective provides a more coherent understanding of conditions such as type 2 diabetes mellitus, obesity, atherosclerosis, and ageing-related disease, which frequently coexist and interact within the same patient. The integration of additional components—such as vascular dysfunction, gut microbiota, skeletal muscle regulation, and lifestyle factors—further reinforces the concept that chronic disease emerges from **dynamic interactions across multiple systems**, rather than from isolated pathological processes.

From a clinical standpoint, this framework highlights the limitations of traditional organ-based models and supports the need for a more **integrative and systems-oriented approach** in internal medicine. Recognizing shared pathophysiological mechanisms may improve diagnostic reasoning, facilitate the management of multimorbidity, and promote more effective and coherent therapeutic strategies. In particular, the ability to interpret metabolic and inflammatory processes as interconnected may allow clinicians to better identify underlying drivers of disease and to prioritize interventions accordingly.

The translational relevance of this model is evident in its potential applications in risk stratification, preventive medicine, lifestyle intervention, and the identification of upstream therapeutic targets. By linking molecular mechanisms with clinical practice, the metabolic–inflammatory framework offers a bridge between basic science and patient-centered care. This is especially important in healthcare settings characterized by a high burden of chronic disease and limited resources, such as those found in many regions of Latin America, including Mexico, Colombia, and Ecuador.

In addition, the findings of this review underscore the importance of incorporating this integrative perspective into **medical education**. Teaching chronic disease through interconnected biological networks may enhance conceptual understanding, strengthen clinical reasoning, and encourage a more holistic approach to patient care. This may ultimately contribute to the training of physicians capable of addressing the growing complexity of chronic disease in modern healthcare systems.

Finally, the results support the need for continued research focused on the operationalization of this framework in clinical practice. Future studies should explore how metabolic–inflammatory networks can be translated into practical tools for diagnosis, risk assessment, and treatment, as well as how they interact with social and environmental determinants of health.

In summary, understanding chronic disease through the lens of metabolic–inflammatory networks represents a necessary evolution in internal medicine. This approach not only reflects current scientific evidence but also provides a foundation for more integrated, effective, and patient-centered care in the face of an increasingly complex global burden of disease.

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