Integrated Multi-Axis Model of Organ-Metabolic Dysfunction

Dr. Luis Gómez Peña[1]

[1]National University of the East

ORCID ID: https://orcid.org/0000-0001-6323-5075

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Abstract: The Integrated Multi-Axis Model of Organ-Metabolic Dysfunction (MIDOM) is proposed as an innovative approach to understanding the early progression of low-grade systemic inflammation before established organ damage, integrating the intestinal, metabolic, inflammatory, and hemodynamic axes. The *general objective* of the study is to develop and substantiate an integrative clinical model that allows for the early identification of subclinical biological dysfunction and improves intervention capacity in primary care. *Methodologically,* it is based on an integrative theoretical review of recent evidence, articulating functional and biochemical biomarkers at progressive levels of pathophysiological alteration, organized in a multi-axis system with sequential and relational logic. *The main results* show that initial intestinal dysfunction, expressed by alterations in the mucosal barrier, is associated with the development of insulin resistance and, subsequently, with systemic inflammatory activation and endothelial dysfunction, configuring a dynamic and bidirectional process. Furthermore, a positive feedback loop is identified between these axes that amplifies the progression of metabolic damage. *In conclusion,* the MIDOM model offers a solid and clinically applicable conceptual framework for the early detection of low-grade systemic inflammation, with the potential to improve medical decision-making, optimize preventive strategies, and serve as a basis for future clinical validations and technological developments in health.

Keywords: *Low-Grade Systemic Inflammation, Insulin Resistance, Intestinal Permeability, Endothelial Dysfunction, Clinical Biomarkers.*

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I. INTRODUCTION

Identifying and integrating the pathophysiological factors involved in progressive organ and metabolic dysfunction is a fundamental step in anticipating its clinical course and reducing the occurrence of short-, medium-, and long-term complications. The combined analysis of these proximate determinants, primarily linked to metabolism, inflammation, immunity, hemodynamic profile, and gut-organ interaction, allows for a more precise assessment of the patient's actual risk. While neurobehavioral patterns act as distal modulators of organ-metabolic risk, this model prioritizes the evaluation of the pathophysiological mechanisms directly involved in target organ damage. Structuring these elements within the Integrated Multi-Axis Model of Organ-Metabolic Dysfunction (MIDOM) and applying them in clinical practice provides a useful analytical framework for medical decision-making, monitoring disease progression, and individualizing therapeutic strategies.

II. METHODOLOGY

The methodology used to develop the Integrated Multi-Axis Model of Organ-Metabolic Dysfunction (MIDOM) was based on an integrative narrative review of the scientific literature, using recognized health science databases such as PubMed, Google Scholar, and Redalyc. Key descriptors used included “low-grade systemic inflammation,” “insulin resistance,” “intestinal permeability,” “endothelial dysfunction,” and “clinical biomarkers.” From the identified articles, a selection process was carried out based on thematic relevance, methodological quality, and pathophysiological significance, ultimately selecting 14 references that support the proposed model. Of these, 10 (71.4%) correspond to publications from the last five years, while four previous references were included for their conceptual value and pathophysiological foundation. The analysis was based on inductive-deductive and analysis-synthesis theoretical approaches, which allowed for the structuring of an integrative model based on the functional sequence of gut–metabolism–inflammation–hemodynamics. This approach facilitated the construction of a multi-axis conceptual framework, oriented towards understanding the pathophysiological progression and the early identification of subclinical states of organ-metabolic dysfunction.

III. RESULTS AND DISCUSSION

➢ *Integrated Multi-Axis Model of Organ-Metabolic Dysfunction (MIDOM)*

Identifying and integrating the pathophysiological factors involved in progressive organ and metabolic dysfunction is a fundamental step in anticipating its clinical course and reducing the occurrence of short-, medium-, and long-term complications. The combined analysis of these proximate determinants, primarily linked to metabolism, inflammation, immunity, hemodynamic profile, and gut-organ interaction, allows for a more precise assessment of the patient's actual risk. While neurobehavioral patterns act as distal modulators of organ-metabolic risk, this model prioritizes the evaluation of the pathophysiological mechanisms directly involved in target organ damage. Structuring these elements within the Integrated Multi-Axis Model of Organ-Metabolic Dysfunction (MIDOM) and applying them in clinical practice provides a useful analytical framework for medical decision-making, monitoring disease progression, and individualizing therapeutic strategies.

➢ *Anticipation Phenomenon in Reducing the Progression of Organ-Metabolic Dysfunction and its Associated Clinical Events*

The phenomenon of anticipation in medicine is defined as the ability to identify early signs, risk factors, or initial pathophysiological alterations that precede the development of a disease or the onset of clinical complications. This approach allows for the implementation of preventive interventions before the manifestation of significant structural or functional damage to organs or systems of the body. From a clinical and pathophysiological perspective, anticipation involves recognizing evolving risk patterns, integrating clinical, metabolic, behavioral, and environmental indicators, and systematically analyzing these elements to prevent disease progression.

In this context, anticipation is a fundamental component of preventive and personalized medicine, as it guides clinical decision-making toward early and timely interventions with a higher probability of effectiveness. In integrated patient assessment models, anticipation is not limited to detecting disease in its initial stages. It also allows for the estimation of potential trajectories of functional or metabolic decline. This perspective facilitates the timely modulation of pathophysiological processes before the consolidation of irreversible pathological states.

The proposed multi-axis model of clinical assessment incorporates the phenomenon of anticipation as one of its core conceptual foundations. This principle is based on the early identification of behavioral patterns that precede the development of overt disease or the onset of adverse clinical events. Within this approach, patient assessment is not limited to the diagnosis of established pathological states. The model prioritizes the identification of risk factors, incipient physiological imbalances, and evolutionary patterns that foreshadow potential progression to organ dysfunction or chronic disease. This perspective allows for a broader understanding of the patient's clinical trajectory.

From this perspective, the phenomenon of anticipation strengthens the model's predictive capacity. It also guides clinical decision-making toward earlier and more personalized interventions, with the aim of modulating pathophysiological processes in their initial stages. In this way, the multiaxis model not only contributes to improving clinical risk stratification but also promotes a preventive approach focused on limiting disease progression and preserving the body's functionality.

Theoretical modeling, based on the analysis of predicting the risk of progressive damage to target organs such as the brain, heart, liver, and kidneys—considering this risk as an essential category that permeates the entire model—integrates methodological actions aimed at preventing, halting, or delaying the onset of structural and functional dysfunction in these organs. This approach recognizes the systemic and dynamic nature of metabolic organ dysfunction, allowing intervention in subclinical stages before the manifestation of major events. The integration of metabolic, inflammatory, and hemodynamic determinants within a predictive framework facilitates the early identification of at-risk patients, which is useful for guiding clinical strategies aimed at preserving organ function and limiting progression to irreversible damage. This concept aligns with the principles of the *"Anticipation Phenomenon in Medicine,"* prioritizing continuous organ protection from the initial phases of the pathophysiological process.

➢ *Multisystemic Predictive Stratification Axis of Progressive Organic Risk (MIDOM Cascade)*

This section describes the anticipatory function of the model, which aims to systematically identify the risk factors present in the patient. In this context, the pathophysiological cascade proposed by the *Integrated Multi-Axis Model of Organ-Metabolic Dysfunction (MIDOM) will be analyzed*, considering the sequential and dynamic interaction of its different levels. The model integrates and weighs metabolic, inflammatory, and hemodynamic variables, assuming them to be components of an interrelated and evolving system. These levels influence the trajectory of the individual's pathophysiological state, allowing for the estimation of the probability of progression to target organ damage.

The prediction of target organ damage risk is based on initial chronic exposure to *adverse neurobehavioral factors, which act as distal modulators* that influence the individual's baseline physiological state. In early stages, intestinal alterations characterized by changes in the microbiota-host interaction and local immune activation can act as an early modulator that promotes the generation of *pro-inflammatory signals in the mucosa. Early metabolic alterations* subsequently develop on this substrate, establishing a dynamic and interdependent relationship with *systemic inflammatory factors*; together, these domains contribute to the development of *hemodynamic-endothelial alterations* characteristic of the individual's pathophysiological state.

As complementary elements within this network of interaction, these processes contribute to the appearance of early functional and structural alterations in tissues highly sensitive to chronic damage. From this *system of pathophysiological relationships emerges the predictive premise of the model*, allowing for the early identification of the risk of progression to dysfunction in target organs such as the brain, heart, liver, and kidneys, and facilitating the implementation of preventive strategies aimed at modifying the evolutionary course of the disease.

In this context, *neurobehavioral factors*, as part of *Level 1 of the MIDOM cascade*, represented by *insufficient sleep, active smoking, unhealthy diet, physical inactivity, and harmful alcohol consumption*, constitute initial chronic exposures that condition the individual's baseline physiological state upon which the pathophysiological cascade of events and the consequent multi-organ damage develop. Therefore, within the MIDOM model, these factors are recognized as primary exposure elements whose early identification is fundamental to characterizing the starting point of the pathophysiological process and understanding the risk terrain from which the organ-metabolic progression begins. While it constitutes the modulating starting point of risk, its sustained dysregulation behaves as an active pathophysiological domain that perpetuates subsequent levels.

The MIDOM model incorporates a *Level 2 Intestinal Dysfunction*, represented by both *fecal mucus*, an early functional marker of the mucosal barrier, and *fecal zonulin*, considered a key biomarker in the regulation of tight junctions and, therefore, intestinal permeability. At this point in the cascade, the presence or alterations of fecal mucus reflect initial modifications of the intestinal ecosystem induced by previous chronic exposures, demonstrating an early mucosal response. Complementarily, elevated zonulin provides a more specific and quantifiable measure of intestinal barrier disruption, allowing for the objective assessment of "leaky gut" processes in subclinical phases. Together, these two markers constitute an intermediate level of biological vulnerability, in which fecal mucus indicates initial functional changes and zonulin confirms structural alterations of the barrier, facilitating the early identification of progression to states of metabolic dysfunction. Level 2 is not only an early consequence of chronic exposures (Level 1), but also acts as a *point of pathophysiological amplification*, where disruption of the intestinal barrier accelerates the transition to systemic metabolic dysfunction (Level 3).

Observational findings over the past two decades suggest that the gut microbiota may contribute to the metabolic health of the human host and, when aberrant, to the pathogenesis of several common metabolic disorders, including obesity, type 2 diabetes, non-alcoholic fatty liver disease, cardiometabolic diseases, and malnutrition. However, to gain a mechanistic understanding of how the gut microbiota affects host metabolism, research is shifting from descriptive analyses of microbiota censuses to cause-and-effect studies. High-throughput, multi-omics composite analyses of human data, including metagenomic and metabolomic data, along with measurements of host physiology and mechanistic experiments in humans, animals, and cells, have potential as initial steps in identifying possible molecular mechanisms behind the reported associations (1).

Metabolic predictive factors, as components of the model at *Level 3 of the cascade. Metabolic dysfunction* comprises the set of biochemical, anthropometric, and clinical risk variables that characterize an individual's functional metabolic state within a given population. In this research, the triglyceride-glucose (TyG) index is considered an indirect estimator of insulin resistance, the Castelli Index II (CRI-II) is a marker of the atherogenic lipid profile, and abdominal circumference, along with body mass index, are considered indicators of central and total adiposity. An elevated CRI-II score (>3) predicts a higher risk of cardiovascular disease, acute myocardial infarction, and insulin resistance (2). The integration of these factors allows for the early identification of *subclinical metabolic dysfunction states* that promote the activation of systemic inflammatory pathways and constitute the pathophysiological basis for predicting organ-metabolic risk and the progressive development of complications.

The model incorporates the anthropometric considerations established in the 2023 Guidelines for the Management of Overweight and Obesity (3) to strengthen cardiometabolic risk stratification. In this regard, systematic measurement of height and weight is recommended during annual checkups or more frequently depending on the clinical profile for calculating body mass index (BMI). The current cut-off points are adopted: BMI of 25–29.9 kg/m² for overweight and ≥30 kg/m² for obesity, recognizing that a progressive increase in BMI is associated with a higher risk of cardiovascular disease, type 2 diabetes mellitus, and mortality. Additionally, abdominal circumference measurement is indicated to refine the risk assessment, considering values >88 cm in women and >102 cm in men as high-risk.

Similarly, contemporary therapeutic approaches emphasize that lifestyle interventions form the basis for modifying the trajectory of organ-metabolic risk, while pharmacotherapy acts as a strategic modulator in patients with a greater pathophysiological burden. This integrative view aligns with the *therapeutic premise* of the MIDOM model by promoting stepped and personalized interventions based on the patient's profile.

Insulin resistance (IR) and cardiovascular disease (CVD) represent two universal public health risks, especially in contemporary Western societies. A causal relationship linking IR to CVD has been established. The mediating mechanisms are complex, under constant investigation, and not yet fully elucidated. IR is a condition that includes hyperglycemia and compensatory hyperinsulinemia. It occurs when insulin is unable to exert its maximum effect on target tissues, such as skeletal muscle, liver, and adipose tissue. This disruption of insulin signaling pathways leads to the development of cardiometabolic disorders, such as obesity, dyslipidemia, mild inflammation, endothelial dysfunction, and hypertension—all predisposing factors for atherosclerosis and cardiovascular disease (4).

The triglyceride/glucose (TyG) and high-sensitivity C-reactive protein (hs-CRP) ratios can help identify high-risk patients. TyG was categorized at the optimal cutoff value of 8.46, and hs-CRP was categorized at 2.00 mg/L, aligning with the definition of residual inflammatory risk. Controlling inflammation in patients with insulin resistance may provide additional benefits. This approach allows for anticipating progression to cardiovascular disease, metabolic liver disease, and microvascular deterioration, reinforcing the need for integrated predictive clinical models applicable to real-world clinical practice. Modern medicine is moving toward *integrative predictive models that consider the interaction between metabolism, immunity, and tissue inflammation*, a concept known as *Clinical Immunometabolism*. Recent studies have confirmed that chronic inflammation associated with obesity, adipocyte dysfunction, and gut dysbiosis actively participates in the development of insulin resistance and multi-organ damage, including the liver, kidneys, brain, and cardiovascular system (5).

The interaction between insulin resistance and systemic inflammation has been documented as a mediating mechanism of clinical prognosis in vascular diseases (6), reinforcing the interdependent nature of these pathophysiological domains within the proposed model. The triglyceride-glucose (TyG) index, calculated from fasting triglycerides and glucose, is another effective method for assessing insulin resistance. Compared to traditional methods such as the hyperinsulinemic-euglycemic clamp and the homeostasis model assessment of insulin resistance (HOMA-IR), TyG offers the advantages of low cost and easy accessibility (7).

The proper regulation and management of energy, substrate diversity and quantity, as well as macromolecular synthesis and degradation processes, are fundamental for cell and organism survival and health. Cellular and multicellular organization is defended by the immune response, a robust and crucial system that distinguishes self from non-self, recognizes and eliminates pathogenic signals, and protects tissue homeostasis. Multiple levels of evolutionarily conserved interactions occur between the immune response and metabolism. Maintaining this delicate balance is crucial for health and has important implications for numerous pathological conditions, such as obesity, diabetes, and other chronic non-communicable diseases (8).

The proposed model includes a level related to the theoretical assumptions mentioned above. *Level 4 of the MIDOM waterfall Inflammatory Dysfunction (IDD)* is represented by *inflammatory predictive factors* as components that characterize an individual in the presence of systemic immune activation and a chronic low-grade inflammatory state. These conditions frequently emerge as a consequence of underlying metabolic alterations. In this sense, phenomena such as lipotoxicity and glucotoxicity contribute to initiating the inflammatory response. Likewise, adipose tissue dysfunction and the activation of pro-inflammatory signaling pathways act as relevant pathophysiological mechanisms. These processes promote and perpetuate the systemic inflammatory response. Therefore, this level acquires value as a key domain within the MIDOM model for risk stratification.

In this research, high-sensitivity C-reactive protein (hs-CRP) is used *as a marker of humoral hepatic inflammation*. The neutrophil-to-lymphocyte ratio (NLR) is also incorporated as an estimator of *cellular immune imbalance*; an elevated NLR is associated with increased cardiovascular mortality, with a prognostic cutoff point close to 2.5 (9). Complementarily, the systemic inflammation index (SII = Platelets × Neutrophils / Lymphocytes) is used. The latter constitutes an *integrated reflection of inflammatory activation*, cellular immune response, and thrombosis. According to the study by Karaca Y et al. in 2024, the SII, as an indicator of the inflammation-hemodynamic axis, has a cutoff point of 580.49 (10).

Furthermore, the integration of composite biomarkers such as hematological and inflammatory indices and metabolic parameters has shown greater predictive capacity for cardiovascular and renal events compared to isolated markers. The neutrophil-to-lymphocyte ratio (NLR) may reflect the residual risk in patients with atherosclerotic coronary artery disease (CAD). However, in patients with CAD and low-density lipoprotein cholesterol (LDL-C) below1.4 mmol/L, the relationship between the NLR and an unfavorable prognosis is uncertain (11). This finding supports the rationale of the MIDOM approach, where the interaction between pathophysiological domains allows for a more precise estimation of individual risk and promotes precision preventive medicine.

This research considers interleukin-6 (IL-6) as a marker of systemic inflammation of immunometabolic origin, reflecting the activation of the inflammatory axis in subclinical phases and its close relationship with insulin resistance and cardiovascular risk. Tumor necrosis factor-alpha (TNF-α) is also incorporated as an indicator of chronic cellular inflammation and adipose tissue dysfunction, a key mediator in altered insulin response. Elevated levels of both biomarkers are associated with a persistent, low-grade inflammatory state, characteristic of many chronic diseases. Furthermore, the combined assessment of IL-6 and TNF-α allows for an integrated approach to the systemic inflammatory state, making them relevant indicators of the inflammation-metabolism axis and facilitating the identification of risk profiles in the early stages of metabolic dysfunction.

Hemodynamic predictive factors, as part of Level 5 (Hemodynamic-Endothelial Dysfunction) of the cascade, characterize the individual in relation to the functional state of the vascular circulation and the pressure load exerted on the endothelium. In this research, blood pressure is considered the primary variable, as it is seen as a direct indicator of hemodynamic load and sustained vascular stress. Persistently elevated blood pressure reflects alterations in systemic hemodynamic regulation and is closely associated with endothelial dysfunction and vascular remodeling.

The endothelium is involved in the control of vascular tone and homeostasis. Risk factors for arteriosclerosis, as well as other conditions, have been shown to be associated with endothelial dysfunction. Clinically, endothelial function and dysfunction have been primarily assessed by evaluating endothelium-dependent relaxation. The functional implications of endothelial dysfunction in cardiovascular disease are not well defined, but recent clinical trials have suggested that endothelial dysfunction can affect vascular tone and organ perfusion, particularly during stressful situations such as exercise. Furthermore, endothelial dysfunction may represent an early event in the development of arteriosclerosis (12). According to the literature, the cutoff criterion used was 130-80: SBP ≥ 130 mmHg and/or DBP ≥ 80 mmHg (13). Endothelial dysfunction is currently recognized as a key transition point between subclinical metabolic alterations and structural target organ damage, validating its inclusion within sequential models of risk progression.

In the author's view, a dynamic unity of pathophysiological interaction exists among the *predictive metabolic, inflammatory, and hemodynamic factors*, in which equilibrium can be maintained as long as each component remains functionally compensated. This unity is transient, since when metabolic factors are altered, as occurs in insulin resistance, dyslipidemia, or visceral adiposity, they favor the activation of inflammatory factors, which generates amplification of the immunometabolic response. In turn, the persistence of the inflammatory state contributes to endothelial dysfunction and hemodynamic alteration, expressed as elevated blood pressure. When this interaction loses its equilibrium, a pathological potentiation relationship emerges among the three groups of factors, contributing to the pathophysiological contradiction that drives the progression toward damage in target organs. In another sense, each of these components can independently initiate the *Progressive Multi-Organ Metabolic Damage Cascade*. However, it is their sustained interaction that determines the magnitude of the clinical risk and constitutes the basis for the *predictive premise* within the model.

To enhance the explanatory power of the MIDOM model, a bidirectional and cyclical interaction between its components is recognized, forming a "pathophysiological amplification axis." In this axis, insulin resistance (Level 3) acts as an initial trigger that promotes the activation of systemic inflammation (Level 4). In turn, persistent degradation contributes to the deterioration of endothelial function (Level 5), leading to alterations in perfusion and vascular homeostasis. Conversely, endothelial dysfunction perpetuates and exacerbates insulin resistance, thus completing a positive feedback loop that favors disease progression. This dynamic behavior of the model justifies the need for comprehensive and simultaneous interventions at all three levels, with the aim of interrupting the pathological circuit and modifying the evolutionary course of organ-metabolic dysfunction.

From the *dynamic interaction* between *metabolic, inflammatory, and hemodynamic components* emerges a higher-order component called *neuroendocrine dysfunction and target organ damage (DOD),* which corresponds to *Level 6 of the MIDOM cascade* and represents the *integrated clinical expression of systemic functional impairment*. This axis can be prevented or mitigated through the timely identification and control of the three levels described above, thus helping to avoid progression to clinical stages with a higher probability of irreversible structural and functional complications. Its components include cerebrovascular and neurodegenerative diseases, ischemic events, arrhythmias and hypertrophy of cardiac chambers, glomerular filtration rate (GFR) as an expression of renal function, and liver transaminase levels (ALT/AST) as indicators of hepatic and metabolic integrity.

While the model focuses on the progression to target organ damage, it recognizes that, once established, this damage perpetuates previous levels, thus closing a cycle of irreversible progression. Together, these components constitute the advanced clinical manifestation of systemic imbalance and guide prognostic stratification within the model. The *predictive premise arises from the interaction between these components* (Figure 1).

Fig 1 Predictive Premise
(Source: Own Elaboration)

Therefore, the *predictive premise of the model is conceived* as the functional unity among the individual's metabolic, inflammatory, and hemodynamic factors, where the progressive dysregulation of these systems favors early organ dysfunction. In this context, it becomes necessary to maintain control of those modifiable factors through clinical, nutritional, and behavioral interventions, since the sum of metabolic alterations, chronic low-grade inflammatory activation, and endothelial dysfunction promotes progression toward structural and functional damage to target organs. Consequently, *neuroendocrine dysfunction and target organ damage emerge as the pathophysiological integrator of the process*. Therefore, integrating these components into a multi-axis predictive score that estimates the risk of progressive organ-metabolic damage constitutes the distinctive and applicable element of the model in clinical practice.

Overall, the MIDOM cascade is structured into six sequential and interdependent levels that allow for an orderly understanding of the progression of organ-metabolic risk. This approach integrates everything from initial exposures to the clinical expression of damage, facilitating a continuous pathophysiological interpretation of the process. The hierarchical organization not only clarifies the timing of events but also allows for the identification of critical points for preventive and therapeutic intervention. The following is an integrated summary of the six levels that comprise the operational architecture of the model.

- *Level 1. Neurobehavioral Factors:*
  These factors encompass the individual's lifestyle habits and patterns (diet, sleep, physical activity, stress, and alcohol consumption) that shape the biological terrain upon which metabolic and inflammatory alterations develop. They act as the starting point for modulating risk.

- *Level 2. Intestinal Barrier Dysfunction I:*
  It represents the functional state of the intestinal barrier and the microbiota-host interaction. Alterations in the mucosal ecosystem and local immune activation are reflected indirectly by findings such as fecal mucus or directly by fecal zonulin, which can promote pro-inflammatory signals that precede or potentiate systemic metabolic dysfunction.

- *Level 3. Metabolic Dysfunction:*
  This includes alterations in energy, carbohydrate, and lipid metabolism, such as insulin resistance, central adiposity, and an atherogenic profile. This level constitutes the core of organ-metabolic dysfunction and promotes the activation of low-grade inflammatory pathways.

- *Level 4. Inflammatory Dysfunction:*
  It is characterized by the presence of chronic low-grade inflammation and immune imbalance, evidenced by acute-phase reagents and hematological markers. In this phase, the amplification of biological damage is consolidated, linking the metabolic disorder with vascular and tissue dysfunction.

- *Level 5. Hemodynamic Dysfunction:*
  This level encompasses functional alterations of the vascular system, including elevated blood pressure and endothelial dysfunction. It reflects the functional impact of inflammation and altered metabolism on organ perfusion and integrity.

- *Level 6. Neuroendocrine Dysfunction and Target Organ Damage (TOD):*
  It represents the final clinical and subclinical expression of the process, manifested as structural or functional compromise of target organs such as the heart, brain, kidneys, and liver. It constitutes the design of the pathophysiological cascade and the main objective of risk stratification.

In summary, the model constitutes an integrative analytical framework that allows for progressive, systematic, and clinically useful risk stratification. Its application facilitates the early detection of subclinical alterations, guides the prioritization of interventions, and strengthens individualized decision-making in medical practice. Thus, the model not only describes the pathophysiological sequence of organ-metabolic damage but also positions itself as a predictive tool with the potential to improve disease progression monitoring and the prevention of short-, medium-, and long-term complications.

➢ *Comprehensive Intervention Axis for the Modulation and Reversal of Biological Risk*

This section defines the operational component of the model, which focuses on structured and deliberate clinical action. It is based on the coherent integration of non-pharmacological and pharmacological interventions, applied in a personalized manner according to the patient's profile. These interventions aim to correct metabolic dysregulation and reduce systemic inflammation, with the goal of preserving the functional integrity of target organs and preventing their progressive deterioration.

The *prediction of the risk of progression of metabolic and organ damage*, within the MIDOM model, is based on the *dialectical relationship between non-pharmacological and pharmacological treatment* as complementary and interdependent components of the clinical approach. Non-pharmacological treatment is conceived as the basic premise of cross-cutting intervention, aimed at modulating neurobehavioral determinants early on (Level 1), promoting the balance of the intestinal mucosal ecosystem (Level 2), correcting metabolic alterations (Level 3), attenuating systemic inflammatory activation (Level 4), and optimizing the hemodynamic-endothelial profile (Level 5), with the ultimate goal of preventing or delaying neuroendocrine dysfunction and target organ damage (Level 6).

For its part, pharmacological treatment is incorporated as a strategic support component, indicated when the pathophysiological burden exceeds the body's adaptive capacity or when it is necessary to enhance, accelerate, or sustain the therapeutic effects achieved. From the dynamic interaction between both approaches emerges a functional synthesis that strengthens the model's coherence, allows for the standardization of medical actions, and, at the same time, facilitates personalized management according to the patient's risk profile, thus consolidating the integrative therapeutic premise as the cornerstone of the contemporary clinical approach.

Non-pharmacological treatment, as a structural component of the MIDOM model, is conceived as an organized and stepped set of therapeutic interventions based on physiology and the body's self-regulating capacity, aimed at modulating the different levels of the pathophysiological cascade. This *approach acts transversally within the patient's daily environment:* lifestyle modifications and sleep hygiene primarily impact neurobehavioral determinants (Level 1); optimization of intestinal function and modulation of the microbiota target Level 2; therapeutic nutrition and control of body composition affect the metabolic axis (Level 3); while planned physical activity and stress management strategies contribute to attenuating inflammatory activation and improving the hemodynamic-endothelial profile (Levels 4 and 5). Taken together, this continuous action system promotes metabolic stability, reduces low-grade inflammation, and protects the functional state of target organs, and also forms the *basis on which pharmacological treatment can be synergistically integrated when the pathophysiological burden requires it*.

The pharmacological interventions, as components of the MIDOM model, represent the set of therapeutic actions prescribed by healthcare professionals to *specifically modulate pathophysiological mechanisms* across the six levels of the cascade. Their implementation is conceived as strategic support when non-pharmacological measures require clinical enhancement or when the pathophysiological burden demands it. At Level 1, medications may be used to manage sleep disorders, smoking/alcohol cessation, healthy eating, physical exercise, and mindful breathing; at Level 2, therapies aimed at modulating the gut ecosystem (such as specific probiotics or nutraceuticals like L-Glutamine, based on clinical judgment); at Level 3, pharmacological optimization (Metformin and Omega-3) to regulate insulin sensitivity, lipid profile, and excess adipose tissue; At Level 4, anti-inflammatory and immunomodulatory strategies are used according to the clinical context, such as Omega-3 fatty acids and zinc; at Level 5, pharmacological control of blood pressure and endothelial function is implemented; and at Level 6, specific management of the manifestations of target organ damage and the neuroendocrine-organ axis is provided. This *stepwise approach* contributes to *systemic functional stabilization* and the *reduction of clinical risk progression* within the *model's integrative framework*.

The relationship established between *non-pharmacological treatment, conceived as a baseline therapeutic premise, and pharmacological treatment, understood as specialized clinical support,* constitutes a *dialectical pair characterized by a dynamic functional dependence.* Non-pharmacological interventions shape the physio metabolic state upon which drugs act, conditioning their indication, intensity, and duration; while pharmacological treatment enhances, stabilizes, or corrects those alterations that exceed the biological regulatory capacity achieved through baseline measures.

Depending on the degree of clinical response resulting from the integration of both approaches, the systemic inflammatory state, insulin sensitivity, body composition, and stability of the neuroendocrine-organ axis can be modified. This axis is understood as the integrating system of nerve, hormonal, and metabolic signals that regulate systemic homeostasis, and its sustained dysregulation is a central mechanism in the progression to target organ damage. This approach allows for individualized adjustment of the therapeutic strategy and optimization of the patient's metabolic prognosis.

The *dialectical contradiction between the therapeutic components of the model* arises because, while non-pharmacological treatment acts as a universal basis applicable to most patients through interventions on intestinal and metabolic therapeutic nutrition, microbiota modulation, structured exercise, neuroendocrine regulation, and optimization of body composition (which constitutes one of the opposing elements in the functional unity of the system), pharmacological treatment introduces individualized therapeutic differentiation. That is, while the non-pharmacological basis tends to homogenize the metabolic pathophysiological terrain, pharmacological interventions—insulin sensitizers, modulators of the gut-metabolism axis, indirect metabolic anti-inflammatories, and drugs used in selected clinical profiles—generate specific therapeutic responses according to the clinical phenotype, the degree of inflammation, insulin resistance, and the presence of comorbidities, thus shaping the dynamic of opposition and complementarity inherent in the model.

From the interaction between *non-pharmacological treatment as the structural foundation of the approach and pharmacological treatment as a specific modulator of clinical risk*, a higher-order component emerges: *comprehensive therapeutic coherence*. This coherence promotes the alignment of clinical interventions toward a single pathophysiological objective, allowing actions on the metabolic, inflammatory, and intestinal terrain to maintain continuity and synergy over time. The functional relationship between both components gives rise to the *integrated therapeutic premise*, in which the non-pharmacological foundation supports the patient's biological stability, while pharmacological support optimizes and adjusts the clinical response according to the individual evolution of risk.

The therapeutic premise is conceived *as the clinically identifiable therapeutic windows* within the MIDOM cascade, during which the healthcare professional has a temporary opportunity to intervene in a targeted manner, with the aim of modifying the pathophysiological trajectory and preventing progression to levels of greater complexity and target organ damage. The coherence and logical sequence between both levels of intervention (non-pharmacological and pharmacological) promote the deceleration of progressive damage to target organs and the stabilization of the patient's pathophysiological state; therefore, the standardization of these components within a comprehensive therapeutic protocol allows for the systematic monitoring of clinical, metabolic, and inflammatory outcomes within the context of the proposed research model. The six therapeutic windows for intervention, according to predictive levels, are revealed below.

- *Therapeutic Window 1 --- Neurobehavioral Reprogramming. (Level 1: Neurobehavioral):*

These correspond to the intervention period focused on behavioral determinants and biological rhythms. This phase prioritizes actions aimed at sleep hygiene, smoking and alcohol cessation, improved eating patterns, increased physical activity, and stress management, with the goal of reducing the initial chronic exposures that trigger the pathophysiological cascade.

- *Therapeutic Window 2 --- Modulation of the Intestinal Ecosystem. (Level 2: Mucosal Barrier / Fecal Mucus):*

It focuses on restoring the balance of the intestinal mucosal ecosystem and barrier function. It includes strategies for microbiota modulation, intestinal nutritional support, and dysbiosis management, with the aim of reducing pro-inflammatory signals of enteric origin that precede systemic metabolic alterations.

- *Therapeutic Window 3 --- Early Metabolic Correction. (Level 3: Metabolic):*

Aimed at controlling insulin resistance, central adiposity, and the atherogenic lipid profile. This stage integrates nutritional and pharmacological interventions, when appropriate, and weight reduction strategies to prevent the consolidation of subclinical metabolic dysfunction.

- *Therapeutic Window 4 --- Containment of Systemic Inflammation. (Level 4: Inflammatory):*

Focused on attenuating low-grade chronic inflammation and immune imbalance, this approach includes intensive metabolic optimization, anti-inflammatory interventions, and control of perpetuating factors to interrupt the amplification of the pathophysiological cascade.

- *Therapeutic Window 5 --- Hemodynamic and Endothelial Protection (Level 5: Hemodynamic-Endothelial):*

Focused on controlling blood pressure, vascular function, and endothelial stability. Includes pharmacological and non-pharmacological measures to reduce hemodynamic burden and prevent the transition to structural organ interventions.

- *Therapeutic Window 6---Mitigation of Organ Neuroendocrine Damage. (Level 6: Organ-Neuroendocrine Axis / DOD):*

These correspond to the intervention phase regarding the clinical expression of target organ damage. It focuses on the comprehensive management of cardio-reno-metabolic and neuroendocrine complications, with strategies aimed at limiting progression, improving organ function, and optimizing prognosis.

The comprehensive intervention strategy for modulating and reversing biological risk is conceived as the *operational component of the MIDOM model*, designed to act in a timely and sequential manner on the different levels of the pathophysiological cascade. The therapeutic premise is configured as follows (Figure 2):


Ventanas Terapéuticas

Ventana terapéutica 1
Reprogramación neuroconductual
(Nivel 1: Neuroconductual)
Higiene del sueño, cesación tabáquica, mejera del patrón alimentario, incremento de la actividad fisica y manajo del estres.

Ventana terapéutica 2
Modulación del ecosistema intestinal
(Nivel 2: Barrera mucosa / moco fecal)
Modulación de microbiota, manajo de disbiosis y soporte nutricional intestinal

Ventana terapeutica 3
Corrección metabolica temprana
(Nivel 3: Metabólico)
Control de resistencia a la insulina, adiposidad central y perfil lipídico aterogénico.

Ventana terapéutica 4
Contención de la inflamación sistémica
(Nivel 4: Inflamatorio)
Optimización metabólica intensiva y estrategia antiinflamatoria.

Ventana terapéutica 5
Protección hemodinámica y endotelial
(Nivel 5: Hemodinámico-endotelial)
Control de la presión arterial y de la función vascular.

Ventana terapéutica 6
Mitigación del daño órgano-neuroendocrino
(Nivel 6: Eje órgano-neuroendocrino / DOD)
Tratamiento de complicaciones cardio-cerebrales y hepato-renales.

Daño Órgano-Metabólico

Fig 2 Therapeutic Premise
(Source: Own Elaboration)

This approach integrates non-pharmacological and pharmacological interventions based on identified therapeutic windows, with the aim of modifying neurobehavioral determinants, restoring intestinal balance, correcting metabolic alterations, attenuating systemic inflammation, and stabilizing hemodynamic function. Its application not only slows the progression of organ-metabolic risk but also promotes functional reversibility when intervention occurs in early stages, thus becoming the strategic core for personalized clinical management and optimized patient prognosis.

The dialectical relationship between the synthesis processes of this modeling becomes evident: *the predictive premise and the therapeutic premise*, which respectively express the anticipated estimation of the progression of organic and metabolic damage over time and the clinical intervention at the patient's current stage. Within this system of relationships, the model's integrative logic emerges as an essential regularity. This logic articulates the early identification of risk with the structured application of therapeutic interventions directed at the organ-neuroendocrine axis and metabolic, inflammatory, and hemodynamic factors, thus guiding clinical decision-making and optimizing outcomes in the patient's evolution (Figure 3).

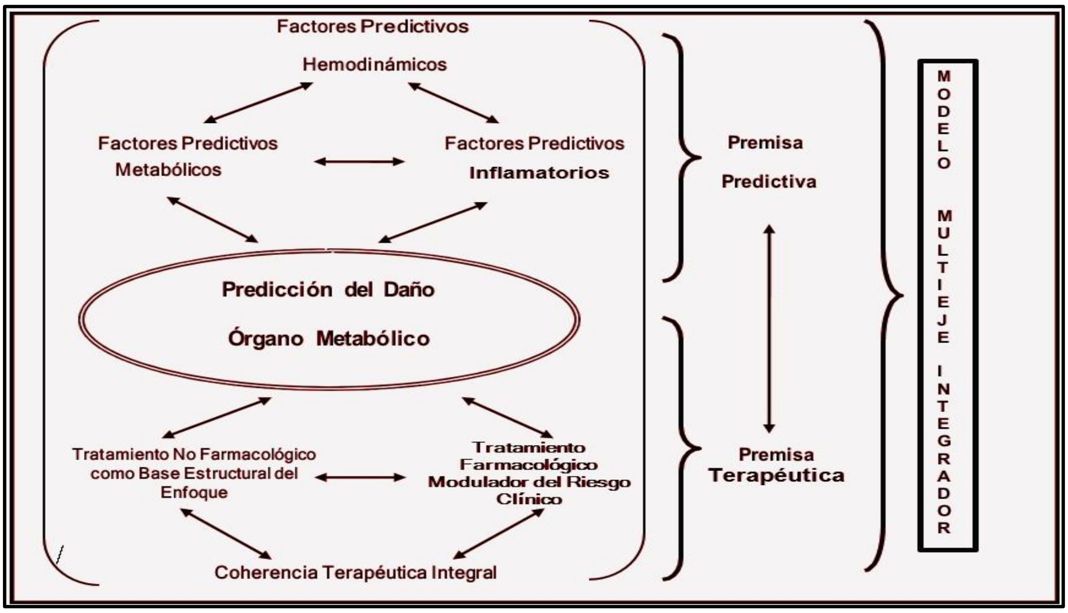

Fig 3 Clinical-Predictive Model
(Source: Own Elaboration)

Overall, the MIDOM model stands out as a conceptual and operational tool consistent with recent advances in clinical immunometabolism. Its systematic application could contribute to slowing the progression of organ-metabolic damage, optimizing therapeutic opportunities, and strengthening stratified preventive medicine. Future longitudinal research will validate its predictive performance and determine its impact in rigorous clinical studies, thus solidifying its potential as an integrative framework for contemporary clinical practice.

The accumulated knowledge of adipose tissue biology and function has driven a significant shift in understanding its role in health and disease. Adipose tissue is now recognized as a crucial regulator of cardiovascular health, mediated by the secretion of various bioactive products, such as adipocytokines, microvesicles, and gaseous messengers, with a wide range of endocrine and paracrine effects on the cardiovascular system. Adipose tissue function and secretome are tightly controlled by complex homeostatic mechanisms and local intercellular interactions, which can become dysregulated in obesity. Systemic or local inflammation and insulin resistance cause a shift in the adipose tissue secretome from an anti-inflammatory and anti-atherogenic profile to a pro-inflammatory and pro-atherogenic one. Furthermore, the interaction between adipose tissue and the cardiovascular system is bidirectional, with signals from vascular and cardiac sources directly affecting adipose tissue biology (14).

Currently, precision medicine applied to the cardiometabolic field is evolving toward approaches that consider the dynamic interaction between multiple pathophysiological processes, rather than analyzing isolated factors. Recent evidence highlights that multivariable models with longitudinal follow-up facilitate the identification of early intervention windows and strengthen the prevention of multi-organ damage. In this sense, these advances provide solid conceptual support for the predictive-integrative approach proposed in the model.

IV. CONCLUSIONS

- The MIDOM model allows us to understand metabolic disease as a dynamic, progressive, and interconnected process, in which intestinal dysfunction acts as the initial event that triggers a pathophysiological cascade.
- It is evident that insulin resistance, systemic inflammation, and endothelial dysfunction are not isolated phenomena, but rather components of a bidirectional

amplification axis that perpetuates damage.

- The incorporation of functional and molecular biomarkers strengthens the predictive capacity of the model by facilitating early detection before evident clinical manifestations.
- The multi-axis approach surpasses traditional fragmented models by proposing an integrative vision applicable in medical practice.
- MIDOM positions itself as a solid conceptual foundation for the development of clinical tools, predictive algorithms, and future scientific validations aimed at the prevention and management of chronic non-communicable diseases.

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