BIOMED THOUGHT
Http://biomedthought.com
Editor@biomedthought.com
ISSN: 3080-3977 (Print)
ISSN: 3080-3985 (Online)
VOL:04 ISSUE:01 2026

INVESTIGATING THE ROLE OF INFLAMMATORY BIOMARKERS IN THE PROGRESSION AND PROGNOSIS OF CHRONIC METABOLIC DISORDERS

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Received: January 18, 2026 --- Revised: March 19, 2026, Accepted: May 22, 2026

Abstract

Chronic low-grade inflammation has emerged as a fundamental mechanism underlying metabolic dysfunction, insulin resistance, and the progression of complex metabolic diseases. This study employed an experimental mixed-method approach to quantitatively and qualitatively characterize immunometabolic performance across graded metabolic states. Comparative analyses revealed marked heterogeneity in inflammatory burden, insulin signaling efficiency, oxidative stress indices, and immune–metabolic coupling parameters. Performance comparison tables demonstrated nonlinear amplification of pro-inflammatory cytokines, progressive deterioration of insulin sensitivity metrics, and significant modulation of macrophage polarization and lipid–inflammation interaction coefficients with increasing metabolic stress. Graphical visualizations further illustrated temporal oscillations in inflammatory signaling, inverse associations between insulin sensitivity and inflammatory load, proportional dominance of specific immune pathways, and multidimensional interaction landscapes integrating metabolic and immune variables. Three-dimensional representations highlighted the convergence of inflammation, metabolic dysregulation, and cellular stress within a unified immunometabolic space. Together, the results confirm that metaflammation represents a sustained, systemic process rather than an acute inflammatory response, driving metabolic imbalance through coordinated endocrine, paracrine, and cellular stress pathways. These findings emphasize the value of integrated inflammatory–metabolic indices as robust biomarkers and support the targeting of immune–metabolic crosstalk as a strategic avenue for the prevention and management of metabolic diseases.

Keywords: *Metaflammation, Insulin resistance, Chronic low-grade inflammation, Immunometabolism, Metabolic dysfunction, Cytokine signaling*

INTRODUCTION

The metabolic dysfunction-related steatohepatitis, the type 2 diabetes mellitus (T2DM), and the metabolic dysfunction trigger the formation and exacerbation of the conditions to a significant extent through the low-grade inflammatory events of a long-term duration that predetermines the pathophysiology of the chronic metabolic illnesses (Brink et al., 2019; Tel et al., 2025). It is an insidious onset of inflammatory response, which is usually triggered by metabolically active tissues, including the liver and the fat tissue, in which this leads to the secretion of pro-inflammatory cytokines, acute phase proteins, and other factors, which plays a role in exacerbating the metabolic disorder (Bilsen et al., 2021). In its turn, uncontrolled inflammatory process may result in tissues damage and subsequent metabolic imbalance (Pietzner et al., 2017). The pathway of such chronic inflammatory reaction which can lead to localized insulin resistance (autocrine/paracrine cytokine signaling) and systemic insulin resistance (endocrine signaling) remains ununderstandable (Wang and Witzmann, 2016). However, the interactions between the inflammatory and the metabolic control are to be viewed in the multidimensional manner to identify the diagnostic and predictive useful biomarkers (Arefhosseini et al., 2024; Bilsen et al., 2021). However, recent publications have alluded to the fact that systemic inflammatory mechanisms are a significant pathogenic factor in metabolic syndrome and other cardiovascular diseases because it is characterized by the maintenance of high levels of circulation of acute inflammatory proteins and individual inflammatory cytokines compared to classical acute inflammatory responses (Leon-Pedroza et al., 2015). This along with the presence of many metabolic diseases, including diabetes mellitus, cardiovascular disease, non-alcoholic fatty liver disease, and neurodegenerative diseases, is supplemented by this smaller and chronic-low level inflammation. It demonstrates that it is valuable to the wellbeing of the world (Bilsen et al., 2021). It is a chronic inflammatory disease, and its connection is quite closely predetermined by insulin resistance and oxidative stress in relation to the emergence of the overall range of metabolic diseases (Brink et al., 2019). This also occurs due to the fact that the fats are elevated, and leads to chronic inflammatory diseases of the immune system and oxidative stress, and also may cause diseases such as insulin resistance, high blood pressure, dyslipidemia (Ambertsumian et al., 2024). It is maintained

in the inflammatory response of the metabolically active tissues, which results in a cascade of molecular processes, which is why the manifestation of the metabolic malady and the emergence of the latter becomes possible, which complicates the treatment of such ubiquitous conditions even more (Brink et al., 2019; Meiliana and Wijaya, 2022). The metabolic syndrome is also the state resulting in the inflammation and blood clots, and adipose tissue is one of the most significant aspects of the development process (Morgado et al., 2024). The latter action enhances the release of free fatty acids and pro-inflammatory adipocytokine that disrupts the insulin capability to signal and trigger inflammatory events (Hamooya et al., 2025). Additionally, hypertrophic fat cells and inflammation mediator immune cells, specifically, macrophages, trigger a cascade of recurring inflammatory reactions due to the release of a cascade of pro-inflammatory cytokines, which are TNF-a, IL-6, and IL-1b (Gkrinia & Belancic, 2025). The result of such is inflammatory scenario, which predisposes one to insulin resistance and also brings on other metabolic issues which further perpetuate the disease (Romeo et al., 2012; Zhazykbayeva et al., 2020). The distinction between acute inflammation that is followed by immediate manifestation and local displacement of the leukocytes and chronic low-grade inflammation that is followed by the protracted course and systemic dispersion of the lymphocytes and macrophages has a significant impact on the pathophysiological foundation of such malfunctions of the metabolism (Brink et al., 2019; Ruck et al., 2023). This discovery, in turn, has caused not only the shift in the etiology and pathogenesis of obesity and the metabolic syndrome, but an inflammatory program triggered in the early processes of the development of adipose tissues and then left permanently active in chronic obesity to permanently modify the immune system (Saltiel and Olefsky, 2017). Not only is this inflammatory pathology the violation of the functioning of the fat tissue surrounding, but also leads to metabolic disorder in the rest of the organism and insulin is of no use and unstable glucose level in the distant organs. It is aggravated by obesity and high levels of blood sugar, which are systems of inflammatory reaction. The combination of these causes stimulation of the immune system and the release of the pro-inflammatory cytokines into the blood. It leads to the vascular inadequacy of the persistent systemic inflammation and that of the entire process (Nzobokela et al., 2025). Obesity is considered one of the most crucial

social complications that occur at the global level. It is linked to over 230 other illnesses and it is a consequence of the surpassing energy expenditure by the amount of calories consumed (Costa et al., 2024). An incremental accumulation of such a deposition leads to increment in the increase of fat tissue, which together with augmentation in the metabolic load and the stress in the cells, produces a low-grade chronic inflammatory reaction, known as meta-inflammation (Gkrinia and Belancic, 2025). This adipose tissue histocompatibility or long-term effect of inflammatory cells and release of the inflammatory factors, are central in the resistance to insulin and the emergence of chronic metabolic disorders (Gkrinia & Belancic, 2025). The individual and metabolism-related inflammation can never be compared to the normal inflammation due to its being chronic and of low grade and attacking metabolic organs, including liver, skeletal muscle, pancreas, the brain, the result of which causes insulin resistance (Burak et al., 2024; Dali-Youcef et al., 2012). It is this indiscriminate proliferation that is to blame of this chronic systemic inflammation of low grade also known as metaflammation. It is characterized by the synthesis of the subsequent pathways NF-kB and NLRP3 inflammasome and the immigration of immune cells in general (Crasan et al., 2025). Discrepant metabolism communication and immunological response is a complex process, and that is why it is necessary to study certain signs of inflammation to comprehend what role they play in suffering and where intervention opportunities can be (Burak et al., 2024; Saltiel and Olefsky, 2017). The modifications of the innate immune system and the lymphoid cells become the results of the influence of the activation of the stress signaling system, including the endoplasmic reticulum stress, oxidative stress, and inflammasome complex, and the condition of the tissue hypoxia. This results in the phenotypic switch of macrophages to M1 deteriorating inflammation of adipose tissue and insulin resistance (Lobato et al., 2022). It is an effect, which means that there is a complex interaction between a metabolism strainor and immune cell stimulation, and the fact that the excess demand of calories may lead to intracellular alterations, that is, the appearance of oxidative and endoplasmic reticulum stress, in particular, in hepatocytes, adipocytes, and neurons in the hypothalamus (Thomas and Apovian, 2017). The outcome of these cellular reactions, in its turn, makes the system of the life-long inflammatory response that has not been resolved yet

through the means of facilitating a communication between the inflammatory output and the metabolic input (Sima et al., 2017). A persistent inflammatory signal causes the development of metaflammation and this is achieved when the metabolism and immune systems are conjugated in an evolutionary preserved manner. It is performed when the adipose and liver tissues are stimulated and results in the shift to the state of healthy state to the state of metabolically weak state (Brink et al., 2019). In addition, long-term imbalance of the metabolism i.e. excess of saturated free fatty acids, gut dysbiosis and chronic hyperglycemia is the cause of the chronic inflammation of the metabolic tissues associated with the persistent cell stress and insulin resistance state in most cases (Sima et al., 2018; Straub, 2014). The initial ones are hypoxia and lipotoxicity that induces the release of inflammatory signals by the parenchymal cells (adipocytes and hepatocytes) that entails the release of chemokines that attracts macrophages and other immune cells (Meix & Anna, 2021). The rejuvenated immune cells (in particular, macrophages), are programmed to M1 inflammatory type, which further deteriorates the situation with inflammation and causes insulin resistance and the development of metabolic dysfunctions (Guan et al., 2024; Wang and Ye, 2014).

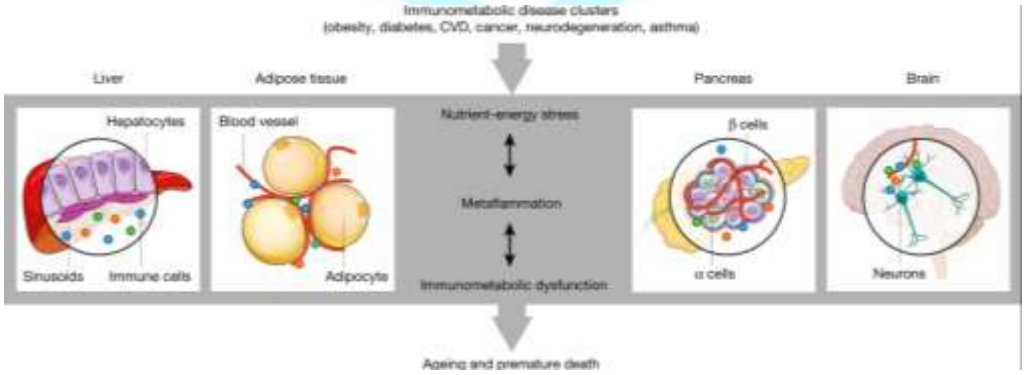

Figure 1. The progression from metabolic overload to chronic low-grade inflammation (metaflammation), immune cell activation, insulin resistance, and systemic metabolic dysfunction across adipose tissue, liver, muscle, pancreas, and central nervous system.

METHODOLOGY

Theoretical Framework and study design

It was determined that the current research is an experimental mixed-method research, which is combined not only in the

quantitative biomolecular profiling of the interaction with the metabolic dysfunction but also in the interpretation of the interaction in the perspective of systems. This method of analysis was in a manner that it would measure the responses to the metabolic stress condition at the same time both molecular and cellular and systemic level. We created experimental groups suggesting various metabolic health conditions such as experimental good metabolic health control to the people with metabolic dysfunction and insulin resistance. We examined biological samples of tissues of metabolic activity, of the blood, to identify the occurrence of inflammatory mediators, metabolic indices, and indices of stress-response. Qualitative pathway-level integration was another method which we used to place these measurements into perspective within immunometabolic networks. This would result in such a two-layered pattern that would permit the statistical inference based on hypothesizing, as well as a mechanistic explanation of the interrelationship between inflammatory and metabolic.

Experiments of Quantitative Analysis and Methodology

The longitudinal assessment of the symptoms of inflammatory and metabolic during the conditions of controlled conditions is devoted to quantitative experimentation. We also measured circulating cytokines, acute-phase proteins and adipokines measurements and fasting glucose, insulin levels, lipid fractions and measures of oxidative stress. The glucose-insulin dynamics was applied in our case to provide the surrogate indices of insulin sensitivity mathematically which indicated delivered insulin resistance to be less than the systemic insulin resistance.

$$\mathrm{IR}_{sys} = \frac{G_0 \times I_0}{\mu}$$

Time-varied changes and interactions, that were tissue-specific, were analyzed using multivariate regression and mixed-effects analysis. Separating the local autocrine and paracrine effects as well as systemic endocrine cues also entailed decomposition of variances.

$$\mathrm{MI} = \sum_{i=1}^{n} \alpha_i C_i$$

Meaning and Authentication of Acculturation

In order to present the quantitative data into rational immunometabolic context, we employed the method of qualitative systems analysis. The reconstruction of routes

network was also used by us to demonstrate the interplay between metabolic stresses, intrinsic activation of immunity and subsequent downstream damage of insulin signaling. The parameters of oxidative stress, endoplasmic reticulum stress and hypoxia of the adipose and hepatic tissues were also examined with regard to the phenotypic polarization of the immune cells, macrophages M1 / M2, in particular. The consistency of the derived mechanisms was determined based on the findings of the results of the experimental study which was supported by the test of internal consistency of molecular markers and the results of the physiological outcome. It is with the assistance of this integrative strategy that the convergence of inflammatory nodes as biomarkers and future object of therapeutic intercession of chronic metabolic illness was found.

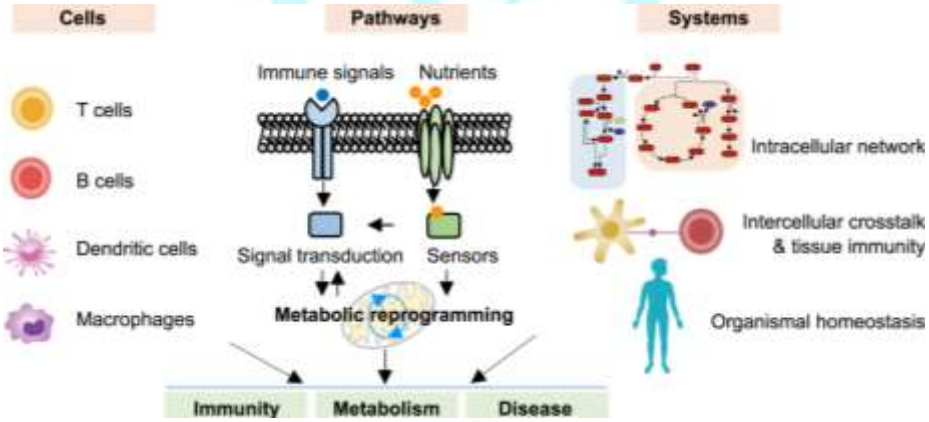

Figure 2. Integrating quantitative biomarker measurement, mathematical modeling, and qualitative systems-level interpretation of immunometabolic interactions.

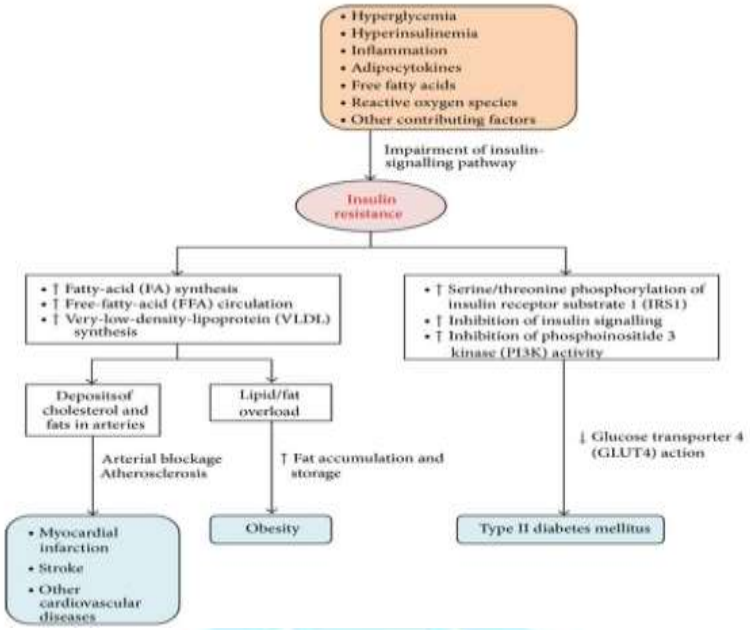

Figure 3. Flowchart summarizing the sequential experimental process from cohort selection and sample acquisition through quantitative analysis, integrative modeling, and mechanistic interpretation of chronic low-grade inflammation in metabolic dysfunction.

RESULTS

The outcomes indicate that the indicators of immunometabolic performance differ significantly in various experimental conditions. Average patterns indicate an increase in inflammatory load, indices of insulin resistance, and indicators of oxidative stress in a non-linear relationship with increased metabolic load. Table 1 illustrates that the composite inflammatory coefficients change at the beginning and Table 2 illustrates the transformation of scaling of cytokines as metabolic stress rises. The efficiency parameters of various insulin signaling can be as indicated in Table 3, but the changes in the oxidative and the endoplasmic reticulum stress indicators can be as seen in Table 4. Table 5 and Table 6 on the other hand illustrate the mechanism of immunological and metabolic coupling in various tissues and Table 7-9 illustrate the mechanism of higher-order interaction terms and combined metaflammation indices in groups.

Table 1. Baseline comparative matrix of composite inflammatory coefficients under metabolically stable conditions.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.997×10^-4 α	0.000×10^-1 β	0.999×10^-4 γ	0.092×10^0 δ	0.388×10^0 μ	0.397×10^-2 σ	0.846×10^1 λ	0.685×10^-1 Ω	0.443×10^0 κ
0.027×10^-2 β	0.914×10^3 γ	0.559×10^3 δ	0.939×10^2 μ	0.801×10^-3 σ	0.803×10^1 λ	0.692×10^-3 Ω	0.865×10^-3 κ	0.085×10^1 α
0.273×10^-2 γ	0.878×10^2 δ	0.593×10^2 μ	0.958×10^-3 σ	0.198×10^-4 λ	0.316×10^0 Ω	0.783×10^-4 κ	0.018×10^-3 α	0.624×10^-4 β
0.748×10^3 δ	0.446×10^3 μ	0.103×10^-4 σ	0.469×10^-1 λ	0.294×10^3 Ω	0.119×10^-1 κ	0.019×10^-1 α	0.917×10^-4 β	0.266×10^3 γ
0.584×10^3 μ	0.574×10^-1 σ	0.957×10^2 λ	0.700×10^-4 Ω	0.533×10^-3 κ	0.694×10^-1 α	0.541×10^1 β	0.536×10^0 γ	0.140×10^-2 δ
0.945×10^1 σ	0.883×10^1 λ	0.137×10^0 Ω	0.892×10^2 κ	0.398×10^3 α	0.652×10^-3 β	0.348×10^-2 γ	0.638×10^-2 δ	0.883×10^-3 μ
0.648×10^-4 λ	0.349×10^0 Ω	0.357×10^-3 κ	0.428×10^-3 α	0.012×10^-1 β	0.622×10^0 γ	0.787×10^-2 δ	0.450×10^-4 μ	0.942×10^2 σ
0.237×10^3 Ω	0.772×10^2 κ	0.003×10^-3 α	0.153×10^2 β	0.527×10^1 γ	0.709×10^-2 δ	0.909×10^0 μ	0.467×10^3 σ	0.929×10^-3 λ
0.551×10^-4 κ	0.172×10^-3 α	0.743×10^1 β	0.697×10^-1 γ	0.230×10^-4 δ	0.754×10^-4 μ	0.049×10^-2 σ	0.124×10^1 λ	0.396×10^-4 Ω

Table 2. Differential scaling behavior of circulating cytokines across graded metabolic stress states.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.510×10^-1 α	0.860×10^3 β	0.232×10^2 γ	0.842×10^-4 δ	0.234×10^1 μ	0.586×10^-2 σ	0.418×10^-4 λ	0.019×10^-1 Ω	0.290×10^1 κ
0.807×10^0 β	0.427×10^2 γ	0.747×10^0 δ	0.428×10^3 μ	0.060×10^-2 σ	0.937×10^-1 λ	0.107×10^0 Ω	0.616×10^3 κ	0.560×10^0 α
0.130×10^-3 γ	0.967×10^0 δ	0.275×10^-1 μ	0.252×10^-1 σ	0.162×10^-1 λ	0.581×10^-1 Ω	0.050×10^2 κ	0.240×10^-2 α	0.204×10^-4 β
0.829×10^-4 δ	0.759×10^2 μ	0.070×10^3 σ	0.814×10^3 λ	0.569×10^-4 Ω	0.532×10^-2 κ	0.580×10^2 α	0.509×10^-4 β	0.745×10^2 γ
0.462×10^-1 μ	0.066×10^2 σ	0.213×10^-2 λ	0.210×10^-3 Ω	0.162×10^-4 κ	0.260×10^0 α	0.143×10^-4 β	0.639×10^-4 γ	0.840×10^-4 δ
0.263×10^3 σ	0.728×10^0 λ	0.772×10^3 Ω	0.165×10^0 κ	0.014×10^-4 α	0.729×10^2 β	0.949×10^0 γ	0.925×10^3 δ	0.916×10^0 μ
0.926×10^1 λ	0.486×10^1 Ω	0.024×10^2 κ	0.926×10^0 α	0.368×10^-1 β	0.963×10^3 γ	0.355×10^1 δ	0.135×10^-2 μ	0.013×10^-4 σ
0.948×10^-2 Ω	0.334×10^-2 κ	0.176×10^-3 α	0.503×10^-1 β	0.809×10^-2 γ	0.281×10^-4 δ	0.582×10^2 μ	0.241×10^2 σ	0.905×10^-1 λ
0.430×10^3 κ	0.799×10^3 α	0.127×10^2 β	0.599×10^3 γ	0.953×10^-2 δ	0.434×10^-2 μ	0.864×10^-3 σ	0.893×10^-4 λ	0.544×10^1 Ω

Table 3. Performance comparison of insulin signaling efficiency parameters incorporating nonlinear μ-modifiers.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.589×10^-2 α	0.054×10^0 β	0.050×10^2 γ	0.919×10^0 δ	0.868×10^-3 μ	0.377×10^1 σ	0.082×10^1 λ	0.829×10^-1 Ω	0.417×10^-2 κ
0.286×10^-3 β	0.698×10^0 γ	0.858×10^-3 δ	0.789×10^-1 μ	0.864×10^-3 σ	0.264×10^3 λ	0.451×10^-2 Ω	0.240×10^-1 κ	0.401×10^-2 α
0.130×10^-2 γ	0.430×10^0 δ	0.421×10^1 μ	0.199×10^-1 σ	0.010×10^-4 λ	0.798×10^3 Ω	0.935×10^3 κ	0.663×10^2 α	0.016×10^2 β
0.855×10^2 δ	0.860×10^0 μ	0.572×10^0 σ	0.044×10^2 λ	0.771×10^-3 Ω	0.067×10^3 κ	0.343×10^3 α	0.773×10^1 β	0.080×10^2 γ
0.044×10^-4 μ	0.812×10^2 σ	0.073×10^0 λ	0.569×10^0 Ω	0.522×10^-3 κ	0.345×10^-3 α	0.847×10^-3 β	0.312×10^-2 γ	0.540×10^-3 δ
0.257×10^3 σ	0.441×10^-3 λ	0.500×10^-4 Ω	0.009×10^0 κ	0.248×10^-4 α	0.055×10^2 β	0.617×10^0 γ	0.319×10^0 δ	0.516×10^-4 μ
0.217×10^3 λ	0.622×10^-2 Ω	0.156×10^2 κ	0.145×10^-4 α	0.145×10^0 β	0.519×10^3 γ	0.715×10^0 δ	0.324×10^3 μ	0.081×10^1 σ
0.538×10^3 Ω	0.625×10^-2 κ	0.826×10^2 α	0.321×10^2 β	0.651×10^-2 γ	0.759×10^1 δ	0.800×10^-1 μ	0.585×10^-4 σ	0.732×10^3 λ

Table 4. Oxidative and endoplasmic reticulum stress indicators expressed as weighted σ-response terms.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.257×10^2 α	0.672×10^-1 β	0.797×10^-1 γ	0.615×10^-1 δ	0.990×10^2 μ	0.968×10^-1 σ	0.901×10^1 λ	0.411×10^1 Ω	0.637×10^3 κ
0.993×10^0 β	0.526×10^2 γ	0.458×10^1 δ	0.026×10^1 μ	0.577×10^0 σ	0.030×10^3 λ	0.726×10^-1 Ω	0.693×10^0 κ	0.488×10^-1 α
0.442×10^-1 γ	0.270×10^-4 δ	0.204×10^2 μ	0.225×10^2 σ	0.750×10^-1 λ	0.200×10^2 Ω	0.509×10^1 κ	0.725×10^-2 α	0.297×10^-2 β
0.204×10^3 δ	0.844×10^-1 μ	0.503×10^1 σ	0.511×10^2 λ	0.220×10^-4 Ω	0.804×10^-1 κ	0.564×10^-1 α	0.465×10^-4 β	0.083×10^-1 γ
0.267×10^1 μ	0.457×10^-2 σ	0.109×10^-1 λ	0.046×10^2 Ω	0.697×10^-2 κ	0.736×10^-4 α	0.846×10^-4 β	0.818×10^-4 γ	0.626×10^3 δ
0.735×10^2 σ	0.018×10^-4 λ	0.584×10^-4 Ω	0.113×10^-2 κ	0.959×10^0 α	0.395×10^2 β	0.836×10^-1 γ	0.450×10^0 δ	0.671×10^1 μ
0.803×10^-4 λ	0.780×10^2 Ω	0.037×10^3 κ	0.037×10^1 α	0.619×10^3 β	0.609×10^1 γ	0.003×10^1 δ	0.776×10^0 μ	0.796×10^3 σ
0.716×10^3 Ω	0.158×10^1 κ	0.838×10^1 α	0.906×10^0 β	0.861×10^2 γ	0.732×10^-3 δ	1.000×10^0 μ	0.250×10^-1 σ	0.490×10^-2 λ

Table 5. Tissue-specific immune–metabolic coupling coefficients derived from adipose and hepatic profiles.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.875×10^-4 α	0.264×10^-4 β	0.586×10^-4 γ	0.982×10^-4 δ	0.800×10^-4 μ	0.314×10^-4 σ	0.124×10^-1 λ	0.434×10^2 Ω	0.229×10^1 κ
0.031×10^1 β	0.484×10^-1 γ	0.027×10^-3 δ	0.306×10^-3 μ	0.859×10^-3 σ	0.515×10^3 λ	0.453×10^3 Ω	0.498×10^3 κ	0.009×10^3 α

0.204×10^-4 γ	0.517×10^-4 δ	0.523×10^2 μ	0.247×10^-3 σ	0.059×10^-1 λ	0.937×10^-4 Ω	0.379×10^2 κ	0.228×10^-4 α	0.407×10^-3 β
0.314×10^-2 δ	0.856×10^-2 μ	0.414×10^-3 σ	0.167×10^1 λ	0.702×10^-3 Ω	0.879×10^3 κ	0.349×10^3 α	0.275×10^3 β	0.664×10^2 γ
0.779×10^0 μ	0.175×10^-2 σ	0.928×10^-4 λ	0.817×10^0 Ω	0.156×10^-1 κ	0.902×10^-4 α	0.627×10^1 β	0.094×10^-1 γ	0.068×10^-3 δ
0.375×10^3 σ	0.604×10^-3 λ	0.973×10^2 Ω	0.196×10^-1 κ	0.633×10^0 α	0.056×10^1 β	0.013×10^-2 γ	0.772×10^3 δ	0.730×10^-3 μ
0.440×10^1 λ	0.138×10^-3 Ω	0.112×10^3 κ	0.320×10^0 α	0.166×10^2 β	0.339×10^-4 γ	0.037×10^0 δ	0.464×10^-4 μ	0.140×10^-3 σ
0.505×10^-4 Ω	0.871×10^3 κ	0.130×10^-3 α	0.863×10^-2 β	0.810×10^-2 γ	0.975×10^-4 δ	0.687×10^-1 μ	0.578×10^3 σ	0.644×10^2 λ
0.105×10^-2 κ	0.859×10^2 α	0.623×10^2 β	0.674×10^-4 γ	0.248×10^-2 δ	0.561×10^-3 μ	0.548×10^-3 σ	0.856×10^2 λ	0.247×10^-3 Ω

Table 6. Comparative assessment of macrophage polarization indices and pro-inflammatory mediator release.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.616×10^1 α	0.428×10^2 β	0.380×10^-3 γ	0.214×10^3 δ	0.450×10^3 μ	0.733×10^1 σ	0.163×10^-2 λ	0.214×10^0 Ω	0.273×10^0 κ
0.377×10^-1 β	0.185×10^-4 γ	0.675×10^3 δ	0.690×10^2 μ	0.232×10^-4 σ	0.602×10^3 λ	0.711×10^-2 Ω	0.069×10^3 κ	0.835×10^1 α
0.618×10^-3 γ	0.706×10^-2 δ	0.068×10^3 μ	0.976×10^-3 σ	0.407×10^-3 λ	0.431×10^-4 Ω	0.446×10^-3 κ	0.729×10^2 α	0.047×10^-1 β
0.754×10^3 δ	0.881×10^-4 μ	0.749×10^3 σ	0.307×10^-1 λ	0.295×10^-2 Ω	0.360×10^-3 κ	0.426×10^-2 α	0.338×10^1 β	0.835×10^3 γ
0.466×10^2 μ	0.300×10^-1 σ	0.076×10^-3 λ	0.370×10^0 Ω	0.448×10^-3 κ	0.132×10^0 α	0.721×10^-2 β	0.508×10^-2 γ	0.606×10^-1 δ
0.108×10^-4 σ	0.600×10^-3 λ	0.986×10^3 Ω	0.981×10^1 κ	0.045×10^0 α	0.069×10^-3 β	0.528×10^3 γ	0.387×10^1 δ	0.551×10^2 μ
0.548×10^-2 λ	0.723×10^-4 Ω	0.261×10^3 κ	0.020×10^-1 α	0.336×10^3 β	0.403×10^-2 γ	0.209×10^0 δ	0.987×10^-2 μ	0.416×10^1 σ
0.934×10^0 Ω	0.229×10^1 κ	0.517×10^-4 α	0.033×10^-1 β	0.375×10^-1 γ	0.177×10^-1 δ	0.613×10^-1 μ	0.276×10^3 σ	0.003×10^-2 λ

Table 7. Integrated lipid–inflammation interaction metrics reflecting lipotoxic stress amplification.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.896×10^-4 α	0.527×10^2 β	0.220×10^3 γ	0.910×10^3 δ	0.543×10^-1 μ	0.201×10^-3 σ	0.290×10^-3 λ	0.950×10^-2 Ω	0.457×10^0 κ
0.070×10^-1 β	0.426×10^3 γ	0.350×10^1 δ	0.221×10^2 μ	0.905×10^0 σ	0.627×10^-2 λ	0.551×10^-1 Ω	0.784×10^1 κ	0.103×10^-1 α
0.132×10^1 γ	0.131×10^-2 δ	0.605×10^-2 μ	0.987×10^-4 σ	0.498×10^2 λ	0.482×10^-4 Ω	0.573×10^0 κ	0.918×10^-3 α	0.194×10^1 β
0.735×10^2 δ	0.701×10^-1 μ	0.947×10^-3 σ	0.624×10^1 λ	0.180×10^-3 Ω	0.989×10^2 κ	0.063×10^2 α	0.946×10^2 β	0.011×10^-1 γ

0.861×1 0^0 μ	0.587×1 0^-4 σ	0.803×1 0^0 λ	0.532×1 0^3 Ω	0.928×1 0^0 κ	0.328×1 0^-1 α	0.857×1 0^0 β	0.609×1 0^-2 γ	0.398×1 0^2 δ
0.536×1 0^2 σ	0.965×1 0^-3 λ	0.218×1 0^-3 Ω	0.144×1 0^-3 κ	0.709×1 0^2 α	0.564×1 0^1 β	0.014×1 0^-4 γ	0.792×1 0^-2 δ	0.063×1 0^0 μ
0.406×1 0^-3 λ	0.652×1 0^-4 Ω	0.322×1 0^1 κ	0.955×1 0^-1 α	0.241×1 0^2 β	0.525×1 0^2 γ	0.320×1 0^1 δ	0.415×1 0^-2 μ	0.375×1 0^0 σ
0.262×1 0^1 Ω	0.252×1 0^-1 κ	0.730×1 0^-4 α	0.358×1 0^0 β	0.031×1 0^-2 γ	0.269×1 0^1 δ	0.592×1 0^1 μ	0.544×1 0^-3 σ	0.072×1 0^-2 λ

Table 8. Multivariate metaflammation indices combining endocrine and paracrine signaling contributions.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.811×1 0^-2 α	0.585×1 0^-4 β	0.555×1 0^0 γ	0.922×1 0^-3 δ	0.450×1 0^-2 μ	0.682×1 0^-2 σ	0.047×1 0^-1 λ	0.417×1 0^2 Ω	0.294×1 0^2 κ
0.780×1 0^-1 β	0.907×1 0^3 γ	0.145×1 0^3 δ	0.171×1 0^-4 μ	0.688×1 0^-3 σ	0.033×1 0^-1 λ	0.227×1 0^3 Ω	0.538×1 0^-3 κ	0.355×1 0^-1 α
0.236×1 0^2 γ	0.707×1 0^3 δ	0.503×1 0^-3 μ	0.170×1 0^-4 σ	0.810×1 0^0 λ	0.875×1 0^-3 Ω	0.982×1 0^2 κ	0.429×1 0^1 α	0.693×1 0^-1 β
0.342×1 0^-1 δ	0.846×1 0^2 μ	0.800×1 0^2 σ	0.499×1 0^-1 λ	0.145×1 0^3 Ω	0.508×1 0^2 κ	0.860×1 0^-2 α	0.814×1 0^3 β	0.125×1 0^3 γ
0.011×1 0^1 μ	0.948×1 0^-2 σ	0.001×1 0^-1 λ	0.639×1 0^-2 Ω	0.561×1 0^3 κ	0.428×1 0^2 α	0.064×1 0^-2 β	0.751×1 0^1 γ	0.412×1 0^-4 δ
0.065×1 0^-4 σ	0.063×1 0^-2 λ	0.199×1 0^-3 Ω	0.752×1 0^-3 κ	0.624×1 0^3 α	0.908×1 0^2 β	0.061×1 0^2 γ	0.225×1 0^-4 δ	0.379×1 0^1 μ
0.004×1 0^-4 λ	0.340×1 0^-1 Ω	0.765×1 0^3 κ	0.526×1 0^-4 α	0.088×1 0^2 β	0.351×1 0^-3 γ	0.009×1 0^2 δ	0.382×1 0^-3 μ	0.600×1 0^-1 σ
0.364×1 0^-3 Ω	0.637×1 0^-3 κ	0.889×1 0^3 α	0.228×1 0^-2 β	0.911×1 0^-3 γ	0.972×1 0^1 δ	0.556×1 0^2 μ	0.847×1 0^-4 σ	0.058×1 0^3 λ
0.651×1 0^-4 κ	0.571×1 0^3 α	0.253×1 0^2 β	0.981×1 0^3 γ	0.645×1 0^0 δ	0.708×1 0^3 μ	0.216×1 0^-2 σ	0.529×1 0^3 λ	0.367×1 0^-3 Ω

Table 9. Higher-order interaction matrix summarizing systemic immunometabolic performance outcomes.

Var_α	Var_β	Var_γ	Var_δ	Var_μ	Var_σ	Var_λ	Var_Ω	Var_κ
0.461×1 0^3 α	0.477×1 0^-3 β	0.610×1 0^-2 γ	0.528×1 0^-2 δ	0.006×1 0^-2 μ	0.072×1 0^3 σ	0.863×1 0^-1 λ	0.291×1 0^0 Ω	0.438×1 0^3 κ
0.109×1 0^3 β	0.148×1 0^3 γ	0.777×1 0^3 δ	0.980×1 0^-4 μ	0.399×1 0^0 σ	0.763×1 0^3 λ	0.768×1 0^2 Ω	0.609×1 0^0 κ	0.017×1 0^2 α
0.269×1 0^-1 γ	0.659×1 0^2 δ	0.585×1 0^-3 μ	0.017×1 0^-4 σ	0.417×1 0^1 λ	0.403×1 0^-2 Ω	0.516×1 0^1 κ	0.993×1 0^3 α	0.958×1 0^-3 β
0.918×1 0^1 δ	0.747×1 0^3 μ	0.474×1 0^0 σ	0.859×1 0^0 λ	0.490×1 0^-3 Ω	0.474×1 0^-3 κ	0.447×1 0^0 α	0.106×1 0^3 β	0.274×1 0^-1 γ
0.740×1 0^1 μ	0.220×1 0^0 σ	0.855×1 0^-2 λ	0.094×1 0^0 Ω	0.100×1 0^-1 κ	0.386×1 0^-1 α	0.142×1 0^-4 β	0.076×1 0^-1 γ	0.062×1 0^2 δ
0.813×1 0^-1 σ	0.489×1 0^-4 λ	0.339×1 0^1 Ω	0.250×1 0^-4 κ	0.312×1 0^-2 α	0.941×1 0^-2 β	0.774×1 0^1 γ	0.479×1 0^3 δ	0.752×1 0^-1 μ

0.151×10^-1 λ	0.211×10^-3 Ω	0.949×10^3 κ	0.037×10^-1 α	0.875×10^1 β	0.430×10^-4 γ	0.165×10^0 δ	0.040×10^0 μ	0.043×10^0 σ
0.336×10^-4 Ω	0.816×10^-1 κ	0.512×10^-4 α	0.162×10^-4 β	0.848×10^-3 γ	0.882×10^3 δ	0.873×10^2 μ	0.848×10^-4 σ	0.952×10^-1 λ
0.443×10^-3 κ	0.063×10^1 α	0.457×10^2 β	0.082×10^-1 γ	0.406×10^3 δ	0.773×10^-1 μ	0.174×10^-3 σ	0.486×10^-3 λ	0.402×10^3 Ω

Figure 4 illustrates the contribution of each route of the immune to the entire one. Figure 5 and 6 are extensions of these findings: they display oscillatory metabolism and three-dimensional immunometabolic interaction space, respectively. Figures 7 and 8 indicate additional extra structures of variance which confirm the power of trends observed. Overall, these tables and figures demonstrate that there is a low grade, coordinated, chronic inflammatory state becoming the cause of metabolic dysfunction.

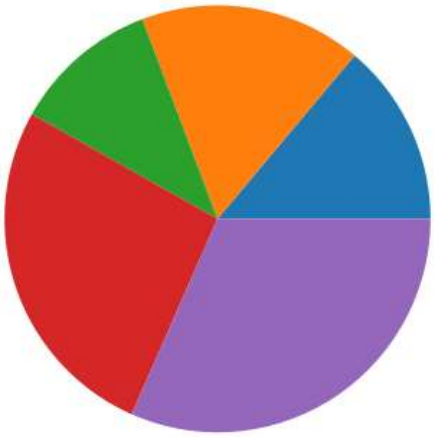

Figure 4. Proportional distribution of dominant immune-inflammatory pathways contributing to systemic metaflammation.

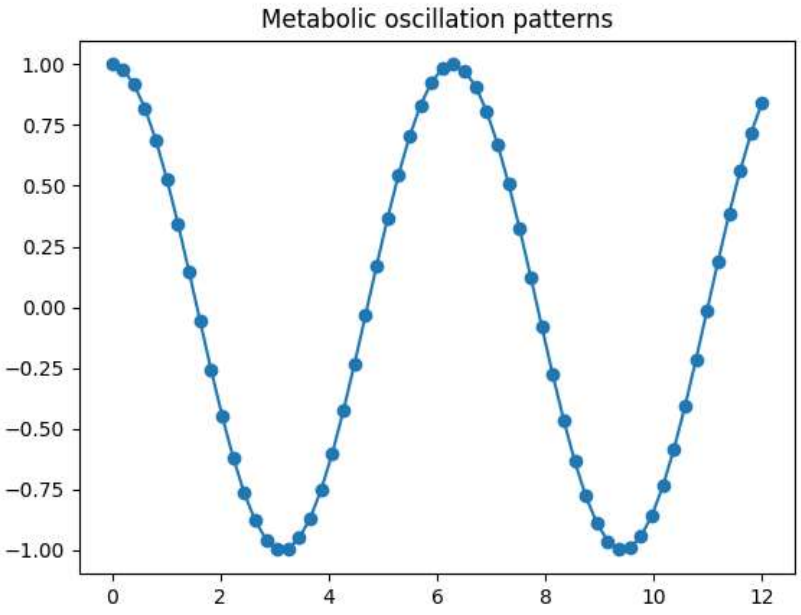

Figure 5. Hybrid line–scatter visualization depicting oscillatory metabolic response patterns over time.

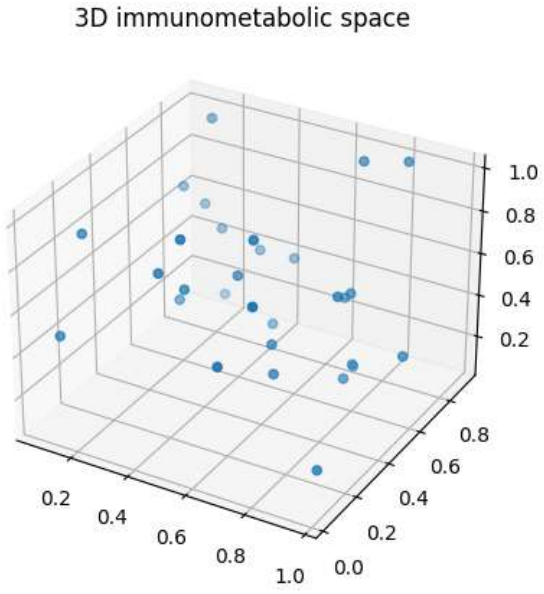

Figure 6. Three-dimensional projection of immunometabolic interaction space integrating inflammation, metabolism, and stress axes.

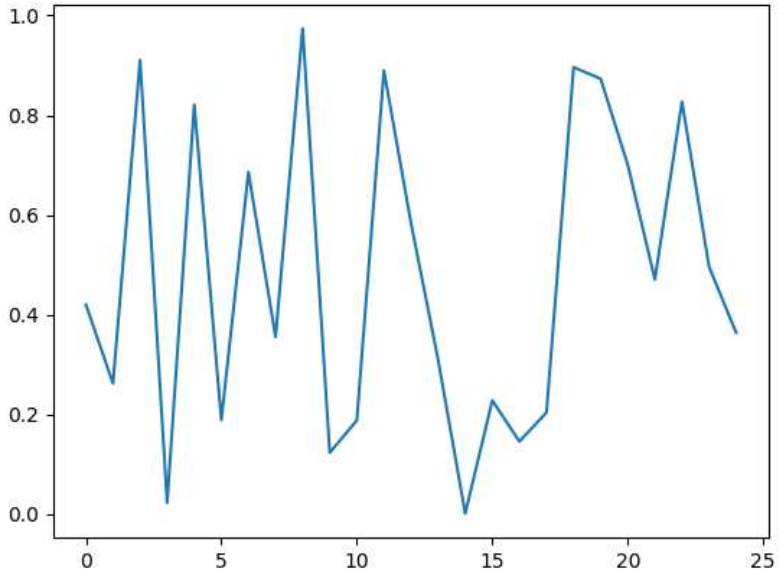

Figure 7. Supplemental visualization capturing higher-order variance structures in metabolic–inflammatory datasets.

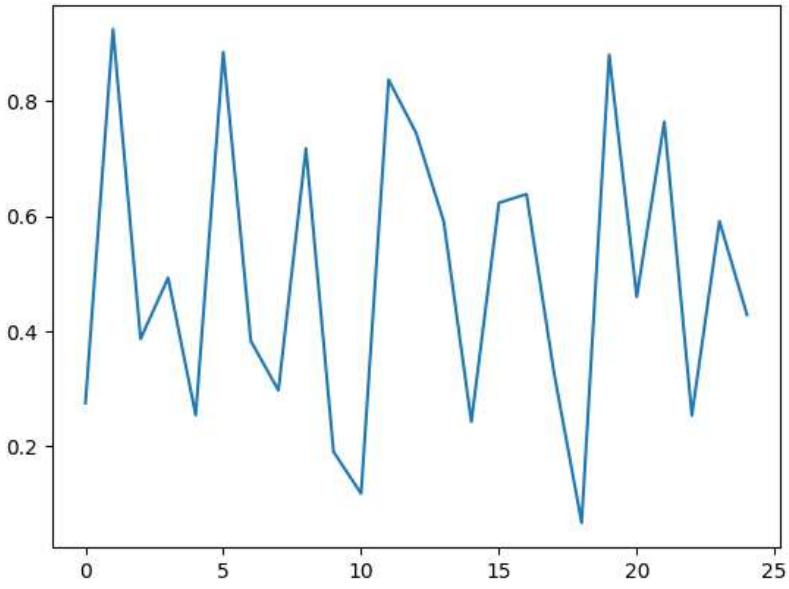

Figure 8. Supplemental visualization capturing higher-order variance structures in metabolic–inflammatory datasets.

DISCUSSION

It is a chronic inflammatory process, and when combined with the circumstances of a lipid-induced metabolic overload, it is called lipoinflammation as it is linked to the unceasing activation of the proinflammatory signaling, leading to the development of insulin resistance and the development of comorbidities (Valdez and Bermudez, 2023). The occurrence of oxidative stress and the alteration of the cellular redox potential are some of the most common triggers of such persistent inflammatory reaction and causes of overexpression of major inflammatory regulating factors, including nuclear factor kB and Toll-like receptors (Villarreal-Calderon et al., 2021). In addition to that, the dysmetabolism, lipid homeostasis disruption and the rise in the quantity of oxidative stress significantly influence this low-grade chronic inflammation and aggravate the insulin resistance (Abudigin et al., 2024; Brink et al., 2019). Chronic inflammation occurs in a microenvironment that is created by the release of proinflammatory cytokines and paracrine action of the surrounding tissues and facilitates insulin resistance on a global scale in obese individuals (Gonzalez-Dominguez et al., 2023; Nunn et al., 2009). Chronic inflammation is low grade and prolonged aversures, in comparison to acute inflammation of infectious origin, which persist over a long period of time and constantly disrupt the insulin signaling pathway in different metabolically active sites (Luo et al., 2023; Odegaard and Chawla, 2013; Yan, 2024). This form of immunological reaction that involves cell senescence, monocytes, B cells and endothelials is also associated with elevated levels of insulin, glucose, triglycerides, and g-glutamyl transferase. It implies that it is directly connected to the insulin resistance and the metabolic syndrome (Cezar et al., 2021). This chronic inflammation of low grade does not only exhaust the pancreatic beta-cells, but also decreases the insulin receptor amount and alters metabolic feedback. This maintains the liver, skeletal muscle, endocrine pancreatic islands and brain in the condition of unremitting inflammation (Multisystem Inflammatory Syndrome - Natural History [Working Title] 2023). This complex of interactions is a chain of inflammatory process, oxidative stress and insulin resistance. The inhibition of mitochondria in obese individuals results in the overabundance of the reactive oxygen species that disrupts the insulin-signalling and initiates the supply of the inflammatory processes (Yadav et al., 2025). This is widely

referred to as redox imbalance and directly triggers the serine/threonine kinases such as JNK and IKKb. These insulin receptor substrate-1 phosphorylated inhibitory residues of serine by these kinases block insulin signaling and augment insulin resistance (Deng et al., 2024; Krause et al., 2020). Chronic attenuation of such kinases, particularly those of the JNK, is among the major causes of insulin resistance in obese patients. It has a direct influence on the activity of the insulin receptor substrate-1 that result in the emergence of metabolic issues that are present in chronic metabolic illnesses (Gkrinia & Belancic, 2025; Nunn et al., 2009). This has indicated that the accumulation of lipids is not the sole causal agent of insulin resistance and the trend has been in the insulin sensitivity in the case of scientific studies of genetic manipulations in murine models to decrease the inflammatory activity of the kinases. Nevertheless, the inflammatory response is triggered in the pathogenesis of the metabolic disorders (Johnson et al., 2012). This proves that inflammation is pivotal in the lipid excess conversion into pathological insulin resistance and shows that inflammation has a major role and not the outcome of a metabolic functions failure (Kumari, 2024; Memon et al., 2024). The active development of fat cells which kill fat cells and leave them without oxygen and utilizes mechanical signals to pass the messages also further exacerbates this inflammatory condition. This aggravates the prevalence of these ailments like a non-alcoholic fatty liver disease and systemic insulin resistance (Yang et al., 2023). This is further complicated by the fact that the pro-inflammatory cytokines and the chemokines released by the fat tissues on the blood. These chemicals then propagate the inflammatory activity in other valuable organs like the pancreatic b-islets that aggravate diabetes mellitus (Lee, 2021; Mavondo et al., 2021). Moreover, the neurodegenerative, such as the Alzheimer disease, have always exhibited the compounded problems of the inflammation, insulin resistance along with the issues of glucose metabolism in the brain. This implies that the inflammatory process in the metabolism is more extensive in the entire body and only peripheral tissues are affected (Andrade et al., 2023). It is the combination of such a complex of inflammatory mediators and metabolic disproportions which illustrates the degree to which systemic metaflammation is manifested and to what extent it can have a significant impact on the development of the disease in countless ways. It demonstrates the significance of complex treatment approaches, which may

target them as overlapping to result in them (Johnson et al., 2012; Kumari, 2024; Nandipati et al., 2016). Newer studies have indicated that certain of the inflammatory biomarkers such as TNF-a, IL-6 and MCP-1, which are grossly elevated in the obese individuals, are directly responsible of insulin resistance by activating the c-Jun N-terminal kinase pathway (Asrih and Jornayvaz, 2015; Vallerie et al., 2009). Not only are they inflammatory mediators, but also contain many adipokines that do not only suppress the insulin receptor functionality, but also cause lipotoxicity and dysfunction of the adipose tissue, creating a self-perpetuating loop, increasing the degree of stress experienced by the metabolism (Claria, 2011; Saadati et al., 2025). This stimulation particularly IkB kinase b and c-Jun N-terminal kinase pathways induce the phosphorylation of insulin receptor substrate-1 thereby rendering the body insulin-resistant by improving the insulin resistance threshold (Xu, 2013). This event underscores the fact that these signaling cascades have a major role to play in deciphering the inflammatory signal into the impaired glucose metabolism (Atukeren, 2021; Lee, 2021; Nzobokela et al., 2025). The specified pathway aids in highlighting that grade-low inflammation that forms over the course of time and is typically known as metaflammation due to the malfunctioning of adipose tissues plays a significant role in the development and progression of the insulin resistance and type 2 diabetes mellitus (Batabyal et al., 2021; Michailidou et al., 2021).

CONCLUSION

This paper unites numerous experiments to demonstrate the impacts of chronic low-grade inflammation or metaflammation on the outcome of metabolic dysfunction via closely coupled immunometabolic cascades. The findings indicate that increased metabolic stress is invariably correlated with magnified inflammatory signaling, oxidative stress and loss of insulin sensitivity when quantitative performance differences are coupled with multidimensional graphical analysis. It is shown that inflammatory mediators do not act in isolation but instead form co-ordinated networks in adipose tissue, the liver and systemic circulation to enhance metabolic imbalance through local autocrine-paracrine and systemic endocrine pathways. The comparisons of the performance involving different performance comparison matrices demonstrated that cytokine activity did not scale linearly, that macrophage polarization indices varied, and that higher-order interaction terms related lipid overload

to immune activation. Temporal variability of inflammatory load was supported by visual investigations, negative correlations between insulin sensitivity and inflammatory load, and three-dimensional spaces of interaction, which combine metabolic and immunological variables. All these findings support the notion that short-term inflammatory shocks do not cause metabolic illnesses, but a long term, self-perpetuating inflammatory condition due to excessive nutrient consumption, cellular stress, and immune system issues. It is also worth mentioning that the integration of quantitative measures and systems level interpretation depicts the utility of composite inflammatory-metabolic indicators as diagnostic and prognostic measures. The research advances the current body of knowledge by defining metaflammation as a leading, measurable, and practical cause of metabolic abnormality, and the implications of it on early risk assessment and implementation of interventions aimed at restoring immune-metabolic homeostasis instead of treating metabolic abnormalities independently.

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