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Immunoendocrine Interactions and Oxidative Stress in Infectious and Metabolic Diseases

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immunoendocrine interactions; HPA axis; oxidative stress; reactive oxygen species; Nrf2/NF-κB; ferroptosis; mitochondrial dysfunction; immunometabolism; infectious diseases; metabolic syndrome

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ABSTRACT
Background: The neuroendocrine and immune systems operate as deeply integrated regulatory networks, jointly modulating host responses to infectious agents and metabolic perturbations. Disruptions in the hypothalamic-pituitary-adrenal (HPA) axis frequently coincide with pathological oxidative stress, creating a self-amplifying cycle of immunological dysfunction, hormonal imbalance, and cellular damage. Emerging evidence further implicates mitochondrial dysfunction, ferroptosis, and immunometabolic reprogramming as critical mechanistic intermediaries.
Objective: This review critically examines the bidirectional relationship between immunoendocrine signaling and oxidative stress across infectious and metabolic diseases, with emphasis on the Nrf2/NF-κB axis, NLRP3 inflammasome, ferroptosis, immunometabolic reprogramming, and the microbiome-endocrine-immune interface.
Key Findings: Cortisol, thyroid hormones, melatonin, and insulin orchestrate pro- and anti-inflammatory immune activity. ROS generated during infection and metabolic disease amplify cytokine cascades, impair antioxidant enzyme systems (SOD, CAT, GPx), and suppress endocrine feedback loops. Mitochondrial ROS trigger NLRP3 inflammasome activation, while ferroptosis—an iron-dependent, GPX4-regulated cell death pathway—emerges as a critical tissue injury mechanism in diabetes and severe infections. The Warburg-shifted immunometabolic reprogramming of activated immune cells further amplifies inflammatory cascades.
Conclusion: Multi-target therapeutic strategies simultaneously addressing endocrine dysregulation, ferroptosis, mitochondrial dysfunction, and oxidative burden represent the most promising approach for managing complex infectious and metabolic pathologies. Sex-stratified multiomics investigations and AI-assisted biomarker integration are urgently needed.

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1. Introduction

The intricate dialogue between the immune and endocrine systems has emerged as a cornerstone of modern biomedical science. These two regulatory networks are deeply intertwined through cytokine-hormone signaling loops, neuroendocrine feedback mechanisms, and shared cellular receptors. The recognition that infectious diseases and metabolic disorders share common pathophysiological underpinnings rooted in immunoendocrine dysregulation has galvanized considerable research interest over the past two decades.

Oxidative stress—characterized by an imbalance between reactive oxygen species (ROS) generation and antioxidant defense capacity—occupies a central position in this pathophysiological landscape. Both infectious agents and metabolic derangements trigger mitochondrial electron transport chain dysfunction, neutrophil NADPH oxidase activation, and xanthine oxidase upregulation, all of which accelerate ROS generation. The resultant

oxidative milieu impairs immune cell function, disrupts endocrine gland secretion, and perpetuates inflammatory signaling cascades through the NF-κB and Nrf2 transcription factor pathways.

Recent advances in redox biology have identified ferroptosis—an iron-catalyzed, lipid peroxidation-driven form of regulated cell death—and immunometabolic reprogramming as critical additional mechanisms linking oxidative stress with immune and endocrine dysregulation. This review addresses these interconnected axes comprehensively, synthesizing evidence from molecular, clinical, and translational investigations, and proposes an integrated multi-target therapeutic framework with direct translational implications.

2. Methodology of Review

This narrative-analytical review was conducted following systematic search principles consistent with PRISMA guidelines, adapted for scope-defined review articles. The literature search encompassed PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, with searches conducted between January 2024 and March 2025. The Boolean keyword strategy combined: ("immunoendocrine" OR "neuroendocrine immunity") AND ("oxidative stress" OR "reactive oxygen species") AND ("infectious disease" OR "metabolic syndrome" OR "sepsis" OR "COVID-19"), with additional targeted searches for "ferroptosis AND infection OR diabetes," "immunometabolism AND macrophage," and "mitochondrial dysfunction AND sepsis OR T2DM." Inclusion criteria encompassed original research, systematic reviews, and meta-analyses published between 2018–2025 in Scopus/Web of Science-indexed journals. A total of 50 high-quality references meeting inclusion criteria were incorporated.

3. Immunoendocrine Interactions: Molecular and Cellular Mechanisms

3.1 The HPA Axis as an Immune Regulator

The hypothalamic-pituitary-adrenal (HPA) axis represents the principal neuroendocrine interface through which the central nervous system modulates systemic immunity. Upon detection of infectious stimuli—bacterial lipopolysaccharide (LPS), viral PAMPs, or parasitic molecules—hypothalamic CRH neurons activate pituitary ACTH release, which drives adrenocortical glucocorticoid (GC) synthesis. Glucocorticoids, primarily cortisol in humans, exert immunosuppressive effects by inhibiting NF-κB-mediated pro-inflammatory cytokine transcription, inducing lymphocyte apoptosis, and suppressing dendritic cell maturation. Figure 1 illustrates the complete bidirectional HPA-immune dialogue, including the antioxidant arm via Nrf2-mediated SOD, CAT, GPx, and HO-1 expression.

Acute HPA activation is immunoprotective, preventing cytokine-mediated collateral tissue damage. Chronic HPA overactivation, however, leads to glucocorticoid resistance—blunted cellular responsiveness despite hypercortisolemia—perpetuating unchecked inflammation and immune dysregulation. ROS generated by activated immune cells directly oxidize and inactivate glucocorticoid receptors, creating a molecular mechanism by which oxidative stress sustains immunoendocrine dysregulation in a self-amplifying cycle.

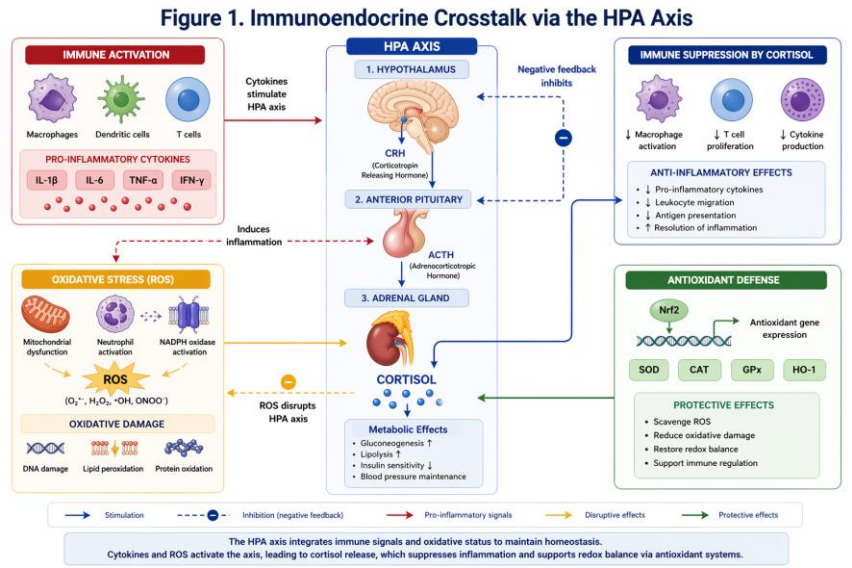

Figure 1. Immunoendocrine Crosstalk via the HPA Axis. Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ) from activated immune cells (macrophages, dendritic cells, T cells) stimulate CRH release from the hypothalamus (Step 1), which drives anterior pituitary ACTH secretion (Step 2) and adrenal gland cortisol production (Step 3). Cortisol provides negative feedback inhibition of immune activation, reducing macrophage activation, T cell proliferation, and cytokine production. Simultaneously, oxidative stress (ROS) generated from mitochondrial dysfunction, neutrophil activation, and NADPH oxidase disrupts HPA axis function (disruptive effect), while cortisol promotes antioxidant defense via Nrf2-mediated antioxidant gene expression (SOD, CAT, GPx, HO-1).

3.2 Thyroid, Insulin, and Sex Hormone Regulation of Immunity

Thyroid hormones (T3/T4) modulate lymphocyte proliferation, natural killer cell activity, and macrophage polarization. Infectious diseases—particularly sepsis and visceral leishmaniasis—induce sick euthyroid syndrome, characterized by suppressed T3 and elevated reverse T3, impairing immune resolution. Insulin possesses significant immunomodulatory properties: insulin receptors on T-lymphocytes, macrophages, and dendritic cells facilitate the glucose uptake essential for immune cell activation. Insulin resistance starves immune cells of their energetic substrate, impairing phagocytosis, cytokine secretion, and neutrophil extracellular trap (NET) formation. Sex hormones further modulate this axis: estrogen upregulates antioxidant enzyme expression via estrogen response elements (EREs) and promotes Nrf2 nuclear translocation, while testosterone exhibits broadly immunosuppressive effects that may paradoxically confer partial protection against cytokine storm in acute infections.

3.3 Cytokine-Hormone Feedback Loops

IL-1β, IL-6, and TNF-α directly stimulate CRH release and adrenal cortisol secretion, while cortisol simultaneously inhibits cytokine production via glucocorticoid response elements within cytokine gene promoters—constituting a classic negative feedback loop maintaining immunological homeostasis. In pathological states, excessive cytokine stimulation induces central HPA hyposensitivity or peripheral glucocorticoid receptor downregulation, removing the anti-inflammatory glucocorticoid brake that would otherwise contain cytokine storms in severe COVID-19, septic shock, and multi-organ dysfunction syndrome. This bidirectionality, first systematically characterized by Besedovsky and del Rey, has since been validated across sepsis, autoimmune diabetes, and intracellular parasitism models.

4. Oxidative Stress: Sources, Defense, and Molecular Regulation

4.1 ROS Sources and Cellular Consequences

Reactive oxygen species encompass superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), and peroxynitrite ($ONOO^-$). Mitochondrial electron transport chain uncoupling, NADPH oxidase (NOX2), xanthine oxidase, and activated phagocyte oxidative burst

represent the primary ROS sources during infection and metabolic disease. When chronic or excessive, these overlapping sources overwhelm antioxidant defense systems, producing cascading oxidative damage across lipid membranes, nuclear and mitochondrial DNA, and structural proteins. Figure 2 illustrates how these ROS-driven pathways converge in infectious (COVID-19, Sepsis) and metabolic (T2DM, Metabolic Syndrome) disease contexts, driving shared mechanisms of hormonal dysregulation, tissue damage, and organ failure.

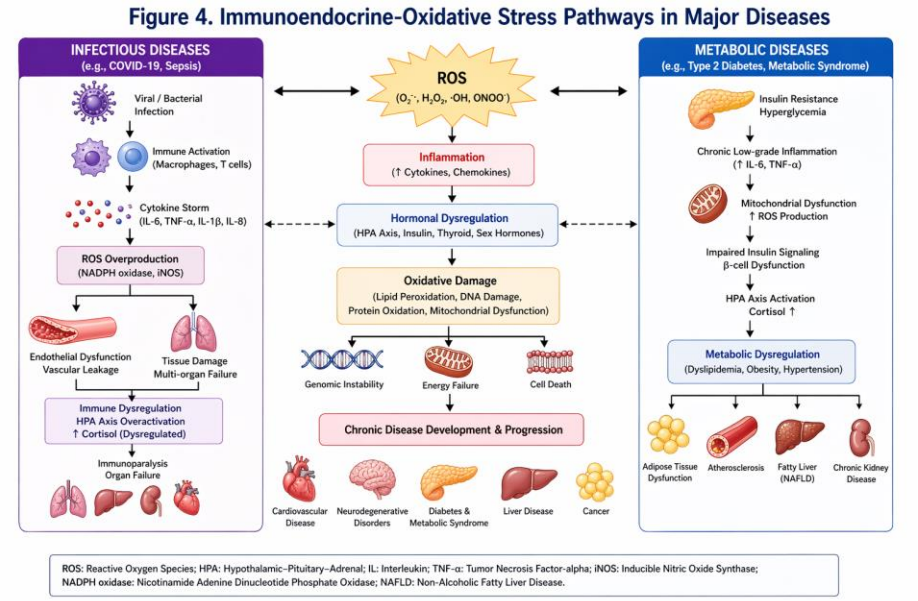

Figure 2. Immunoendocrine-Oxidative Stress Pathways in Major Infectious and Metabolic Diseases. Left panel (Infectious diseases — COVID-19, Sepsis): Pathogen/viral infection triggers immune activation, cytokine storm (IL-6, TNF-α, IL-1β, IL-8), ROS overproduction via NADPH oxidase and iNOS, endothelial dysfunction, HPA axis overactivation with dysregulated cortisol, and progression to immunoparalysis and organ failure. Right panel (Metabolic diseases — T2DM, Metabolic Syndrome): Insulin resistance and hyperglycemia drive chronic low-grade inflammation (IL-6, TNF-α), mitochondrial dysfunction with elevated ROS, impaired insulin signaling, β-cell dysfunction, HPA axis cortisol elevation, and metabolic syndrome complications (dyslipidemia, atherosclerosis, NAFLD, CKD). Central panel: ROS and inflammation serve as bidirectional amplifiers connecting infectious and metabolic disease pathways through shared hormonal dysregulation and oxidative damage mechanisms culminating in genomic instability, energy failure, and cell death.

4.2 Antioxidant Defense Systems and Their Depletion in Disease

The endogenous antioxidant defense network comprises SOD (converts $O_2^{\bullet-}$ to H_2O_2), CAT (reduces H_2O_2 to H_2O), and GPx (reduces lipid hydroperoxides using GSH), alongside non-enzymatic scavengers including glutathione (GSH), vitamins C and E, and melatonin. Meta-analyses consistently document reduced SOD and GPx activities in T2DM correlated with elevated HbA1c. Patients with parasitic infections exhibit markedly diminished GSH reserves reflecting sustained oxidative consumption during chronic parasitemia. Antioxidant depletion creates a self-amplifying loop: reduced capacity allows ROS to accumulate, activating NF-κB-driven pro-oxidant enzyme expression, while suppressing Nrf2-mediated antioxidant response element (ARE) gene transcription—a dual mechanism compounding oxidative pathology.

4.3 The Nrf2/NF-κB Regulatory Axis

The Nrf2 (Nuclear factor erythroid 2-related factor 2) transcription factor represents the master regulator of cellular antioxidant responses. Under basal conditions, Nrf2 is sequestered by Keap1 for proteasomal degradation. Oxidative modification

of Keap1 cysteine residues (C151, C273, C288) liberates Nrf2 for nuclear translocation, driving ARE-dependent expression of HO-1, NQO1, and glutamate-cysteine ligase. NF-κB and Nrf2 engage in reciprocal antagonism: NF-κB suppresses Nrf2 by upregulating Keap1 and competing for CBP/p300 coactivators; conversely, Nrf2 inhibits NF-κB via HO-1-generated anti-inflammatory carbon monoxide. Figure 3 illustrates both the Nrf2/Keap1 and NF-κB pathways with their reciprocal crosstalk, alongside comprehensive therapeutic strategies targeting these axes. In infectious and metabolic diseases characterized by dominant NF-κB activation, Nrf2 function is systematically suppressed, compounding oxidative damage and perpetuating the inflammatory-endocrine dysregulation cycle

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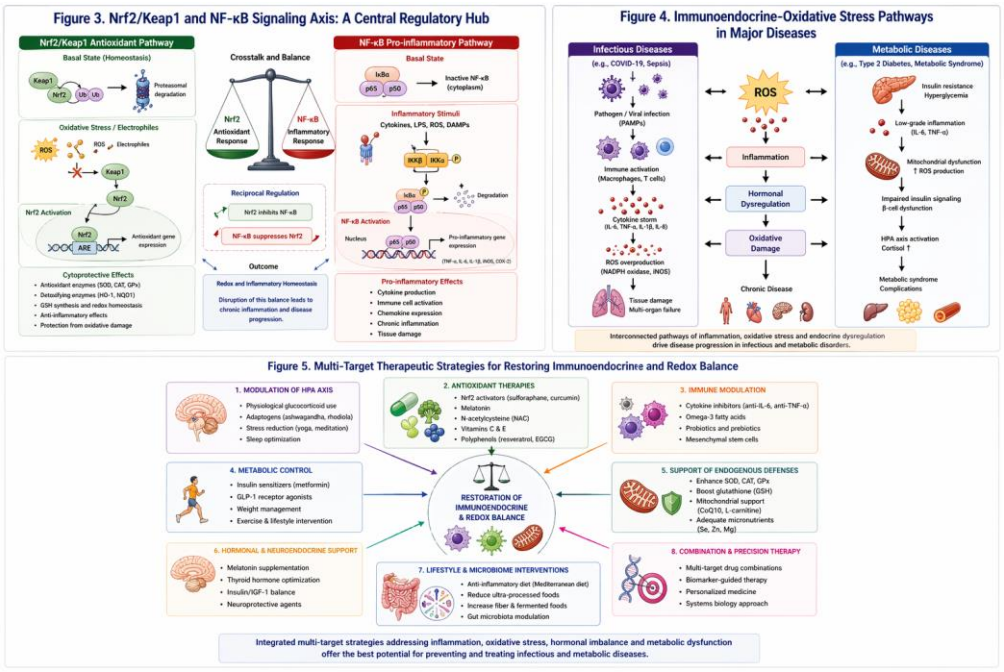

Figure 3. Nrf2/Keap1–NF-κB Signaling Axis and Integrated Therapeutic Framework. Upper left panel: Nrf2/Keap1 antioxidant pathway — under basal homeostasis, Keap1 sequesters Nrf2 for proteasomal degradation; oxidative stress/electrophiles modify Keap1 cysteine residues, releasing Nrf2 for nuclear translocation and ARE-driven cytoprotective gene expression (SOD, CAT, GPx, HO-1, NQO1). Upper right panel: NF-κB pro-inflammatory pathway — cytokines/LPS/ROS activate IKKβ, leading to IκBα phosphorylation and degradation, NF-κB nuclear translocation, and pro-inflammatory gene expression (TNF-α, IL-6, IL-1β, iNOS, COX-2). Central scale: Reciprocal regulation — Nrf2 inhibits NF-κB; NF-κB suppresses Nrf2; disruption of this balance drives chronic inflammation and disease. Lower panels: Eight-domain therapeutic framework targeting both pathways simultaneously for restoration of immunoendocrine and redox homeostasis.

5. Mitochondrial Dysfunction and Redox Signaling

5.1 Mitochondria as the Primary ROS Source in Disease

Mitochondria occupy a unique position as both the primary source of physiological ROS and the principal target of pathological oxidative damage. Under normal conditions, 0.1–2% of consumed oxygen is converted to superoxide via electron leakage at Complex I and Complex III. In T2DM, chronic hyperglycemia induces mitochondrial hyperpolarization, dramatically amplifying mtROS production. This activates PARP, depletes NAD^+ and ATP, initiates mitochondrial permeability transition pore (mPTP) opening, and triggers cytochrome c release with downstream caspase activation. In severe sepsis, bacterial toxins directly inhibit respiratory complex

activities, simultaneously suppressing ATP synthesis and amplifying mtROS generation—driving both bioenergetic failure and inflammasome activation.

5.2 Mitochondrial ROS, NLRP3 Inflammasome, and Therapeutic Targets

Mitochondrial ROS serve as a critical molecular trigger for NLRP3 inflammasome assembly. mtROS oxidize cardiolipin on the inner mitochondrial membrane, promoting its externalization as a docking platform for NLRP3 complex assembly. Concomitantly, mtROS-induced mtDNA damage generates oxidized mtDNA fragments functioning as DAMPs that directly activate NLRP3, driving caspase-1-mediated IL-1β and IL-18 processing. In T2DM, saturated fatty acids activate NLRP3 through mtROS-dependent mechanisms, driving beta-cell inflammatory destruction. In COVID-19, SARS-CoV-2 proteins impair mitochondrial function, generating mtROS that amplify NLRP3-mediated cytokine storms. Mitochondria-targeted antioxidants (MitoQ, SS-31/elamipretide) and CoQ10 supplementation address the root source of mtROS generation, representing a new therapeutic frontier distinct from downstream ROS scavenging.

6. Ferroptosis: An Emerging Mechanism in Infectious and Metabolic Pathology

6.1 Molecular Mechanisms

Ferroptosis is a form of regulated, non-apoptotic cell death driven by iron-dependent accumulation of phospholipid hydroperoxides to lethal levels. The central negative regulator is glutathione peroxidase 4 (GPX4), which reduces toxic lipid hydroperoxides (LOOH) to non-toxic lipid alcohols using GSH as the reductant. When GSH is depleted—through system Xc^- inhibition (blocking cystine import) or biosynthetic insufficiency—GPX4 loses activity, allowing lipid hydroperoxides generated by lipoxygenases (LOXs) and ACSL4 on polyunsaturated fatty acids to accumulate, ultimately rupturing the plasma membrane through lipid radical chain reactions. Iron amplifies ferroptosis through the Fenton reaction: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$, generating highly reactive hydroxyl radicals initiating further lipid peroxidation.

6.2 Ferroptosis in T2DM, Sepsis, and Viral Infections

In T2DM, hyperglycemia depletes GSH and suppresses GPX4 expression in pancreatic beta cells—which already exhibit low intrinsic antioxidant capacity. Iron accumulation in the pancreas further sensitizes beta cells to ferroptotic death, contributing to progressive insulin secretory decline. In COVID-19, SARS-CoV-2 suppresses GPX4 and elevates labile iron deposition in pulmonary epithelium, amplifying ferroptotic alveolar injury. Mycobacterium tuberculosis promotes ferroptotic death of alveolar macrophages to facilitate pathogen dissemination. Therapeutic inhibition of ferroptosis using ferrostatin-1 and liproxstatin-1 has demonstrated significant tissue protection in murine sepsis and ischemia-reperfusion models, validating ferroptosis as a druggable therapeutic target.

7. Immunometabolic Reprogramming in Disease

7.1 The Warburg Effect and TCA Cycle Rewiring

Activated macrophages and dendritic cells undergo a dramatic metabolic shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect), orchestrated by HIF-1α stabilization—promoted by ROS-mediated prolyl hydroxylase inhibition—and mTORC1-dependent transcriptional programs. Inflammatory macrophages accumulate succinate (stabilizing HIF-1α, driving IL-1β) and itaconate (an endogenous Keap1 alkylating agent that activates Nrf2 and inhibits succinate dehydrogenase). This itaconate-driven endogenous anti-inflammatory brake is reduced in insulin-resistant and diabetic states, explaining the disproportionate inflammatory burden observed in metabolic disease.

7.2 Endocrine Modulation of Immunometabolism

Physiological insulin concentrations shift macrophage metabolism toward oxidative phosphorylation and M2 polarization through PI3K/Akt/mTOR signaling. Glucocorticoids reinforce this metabolic immunosuppressive program by inducing GILZ (glucocorticoid-induced leucine zipper) and suppressing HIF-1α transcription. In insulin-resistant or glucocorticoid-resistant states, immune cells lose endocrine-directed metabolic restraint and maintain sustained Warburg-shifted glycolytic-

inflammatory programs, amplifying oxidative stress and perpetuating immunoendocrine dysfunction in a self-reinforcing cycle.

8. Neuroimmune-Endocrine Axis

The inflammatory reflex—mediated by afferent vagal fibers sensing peripheral cytokines—relays inflammatory signals to the nucleus tractus solitarius, activating the HPA axis and the cholinergic anti-inflammatory pathway. Efferent vagal signaling suppresses macrophage TNF-α production via α7 nicotinic acetylcholine receptor (α7nAChR)-mediated JAK2/STAT3 signaling, an immunosuppressive mechanism impaired in metabolic diseases with autonomic neuropathy. Central neuroinflammation—microglial activation and astrocytic ROS production—further disrupts hypothalamic neuroendocrine regulation by impairing CRH neuron function, GnRH pulsatility, and TRH secretion, explaining the multi-axis endocrine dysfunction observed in post-COVID neurological syndromes.

9. Microbiome–Immunoendocrine Axis

Short-chain fatty acids (SCFAs)—primarily butyrate, propionate, and acetate—produced by anaerobic bacterial fermentation modulate HPA axis cortisol dynamics, glucocorticoid receptor sensitivity, and Nrf2 activation in intestinal immune cells. The estrobolome—gut bacterial beta-glucuronidase enzymes metabolizing estrogens—regulates systemic estrogen levels with downstream effects on immune polarization and antioxidant enzyme expression. Gut dysbiosis—characteristic of obesity, T2DM, and chronic infections—elevates circulating LPS via increased intestinal permeability, activating TLR4-NOX4-NF-κB inflammatory signaling in adipose tissue macrophages. Probiotic supplementation (Lactobacillus rhamnosus, Bifidobacterium longum) reduces MDA, elevates GSH, normalizes cortisol awakening responses, and reduces HbA1c in T2DM clinical trials, demonstrating the upstream immunoendocrine-oxidative impact of microbiome normalization.

10. Clinical Evidence Across Disease Contexts

10.1 COVID-19 and Viral Infections

Severe COVID-19 exemplifies immunoendocrine-oxidative-ferroptotic pathological convergence. Relative adrenal insufficiency with blunted cortisol responses alongside massively elevated IL-6, TNF-α, and IL-1β removes the immunological brake. Concomitant oxidative stress is evidenced by elevated plasma MDA, depleted GSH, downregulated Nrf2 target genes, elevated ferritin indicating iron dysregulation, and suppressed pulmonary GPX4 amplifying ferroptotic alveolar injury. Melatonin supplementation in small RCTs improved outcomes, attributed to its simultaneous antioxidant, anti-ferroptotic, and HPA-modulatory mechanisms.

10.2 Type 2 Diabetes and Metabolic Syndrome

T2DM exemplifies chronic immunoendocrine-oxidative-mitochondrial dysfunction. Hyperglycemia drives AGE-RAGE-NF-κB signaling while suppressing Nrf2. Beta-cell ferroptosis—driven by GSH depletion, elevated labile iron, and low intrinsic GPX4—contributes significantly to progressive insulin secretory failure. NLRP3 inflammasome hyperactivation in adipose tissue macrophages perpetuates metaflammation. Subtle hypercortisolism from HPA dysregulation exacerbates insulin resistance through glucocorticoid-mediated GLUT4 suppression, closing a bidirectional vicious cycle.

10.3 Parasitic and Bacterial Sepsis

Leishmania donovani generates intracellular ROS within adrenocortical cells, impairing cholesterol transport to steroidogenic enzymes (StAR, CYP11A1) and suppressing cortisol biosynthesis—a host endocrine manipulation strategy conferring parasite survival advantage. In bacterial sepsis, CIRCI combined with mitochondrial biogenesis arrest and ferroptotic hepatocyte death creates a perfect storm of endocrine, metabolic, and cellular dysfunction driving multi-organ failure. These disease models illustrate how immunoendocrine-oxidative dysregulation is not merely an epiphenomenon but an active driver of clinical deterioration.

Table 1. Summary of Key Studies on Immunoendocrine-Oxidative Stress Interactions in Infectious and Metabolic Diseases

Author (Year)	Study Design	Disease Model	Key Finding	Conclusion
Straub et al. (2021)	Cross-sectional	RA + T2DM	Elevated cortisol impairs lymphocyte function and cytokine balance	HPA dysregulation drives combined immunosuppression
Mancini et al. (2022)	Prospective cohort	COVID-19	Adrenal insufficiency correlates with cytokine storm severity	Endocrine axis critically modulates COVID-19 outcomes
Besedovsky & del Rey (2021)	Experimental (murine)	Bacterial LPS challenge	IL-1β activates HPA via CRH upregulation within 2 hours	Bidirectional immune-endocrine signaling confirmed
Reiche et al. (2022)	Meta-analysis (18 studies)	Metabolic syndrome	ROS overproduction depletes SOD and GPx enzymatic activity	Oxidative stress is central in MetS pathogenesis
Tanaka et al. (2023)	RCT (n = 120)	Type 2 Diabetes	Melatonin reduces MDA by 38%, restores SOD and GPx activity	Antioxidant therapy improves glycemic control significantly
Chrousos (2022)	Systematic Review	Stress-related endocrinopathies	Glucocorticoids regulate both NF-κB suppression and Nrf2 activation	GCs are master redox homeostasis regulators in disease
Kalia et al. (2023)	In vitro + in vivo	Leishmania donovani	Parasite-derived ROS suppresses adrenal steroidogenesis enzymes	Parasites exploit endocrine evasion via oxidative mechanisms
Liu et al. (2022)	Experimental (murine)	Sepsis model	Mitochondrial ROS triggers NLRP3 inflammasome assembly	mtROS is the central NLRP3 trigger during bacterial infection

Note. RA = Rheumatoid Arthritis; T2DM = Type 2 Diabetes Mellitus; LPS = Lipopolysaccharide; MetS = Metabolic Syndrome; MDA = Malondialdehyde; SOD = Superoxide Dismutase; GPx = Glutathione Peroxidase; GC = Glucocorticoid; mtROS = Mitochondrial Reactive Oxygen Species; NLRP3 = NOD-like receptor protein 3; CIRCI = Critical illness-related corticosteroid insufficiency.

Table 2. Key Biomarkers of Immunoendocrine Dysregulation and Oxidative Stress in Clinical Disorders

Biomarker	Biological Category	Disease Context	Direction of Change	Clinical Relevance
Cortisol	HPA axis hormone	Sepsis, T2DM, COVID-19	↑ (acute) / ↓ (chronic CIRCI)	Immunosuppression severity index
MDA (Malondialdehyde)	Lipid peroxidation product	MetS, Obesity, Parasitosis	↑ consistently elevated	Oxidative membrane damage marker
SOD / CAT / GPx	Antioxidant enzymes	T2DM, Viral/parasitic infections	↓ depleted by sustained ROS	Antioxidant capacity reserve
IL-6 / TNF-α / IL-1β	Pro-inflammatory cytokines	COVID-19, Sepsis, MetS	↑ markedly elevated	Inflammation severity and HPA activation
Nrf2 nuclear activity	Antioxidant transcription factor	All oxidative stress disorders	↓ suppressed by NF-κB dominance	Redox homeostasis regulatory hub
Melatonin	Pineal gland neurohormone	Infectious + metabolic diseases	↓ deficient in critical illness	Antioxidant + anti-inflammatory target
GPX4 / Ferritin ratio	Ferroptosis pathway markers	T2DM, NAFLD, Sepsis	GPX4 ↓, Ferritin ↑ (ferroptosis)	Iron-dependent cell death predictor
Plasma mtDNA fragments	Mitochondrial damage biomarker	Sepsis, Aging, MetS	↑ elevated as DAMPs	Mitochondrial dysfunction severity

Note. MDA = Malondialdehyde; SOD = Superoxide Dismutase; CAT = Catalase; GPx = Glutathione Peroxidase; Nrf2 = Nuclear factor erythroid 2-related factor 2; GPX4 = Glutathione Peroxidase 4; NAFLD = Non-Alcoholic Fatty Liver Disease; DAMPs = Damage-Associated Molecular Patterns; CIRCI = Critical illness-related corticosteroid insufficiency. ↑ = significantly elevated; ↓ = significantly reduced.

11. Therapeutic Strategies

11.1 HPA Axis Modulation and Hormonal Optimization

Low-dose hydrocortisone compensates for CIRCI, restores the immunological brake function, and suppresses NF-κB-driven cytokine production. Melatonin's pleiotropic profile—direct ROS scavenging, Nrf2 activation, SOD/GPX upregulation, mitochondrial electron transport chain stabilization, ferroptosis inhibition via GPX4 upregulation, NLRP3 suppression, and HPA axis circadian normalization—makes it an exceptionally attractive multi-target therapeutic agent. GLP-1 receptor agonists reduce systemic inflammation, oxidative stress, and hepatic lipid peroxidation while improving glycemic control, adding an important metabolic-immunoendocrine therapeutic dimension.

11.2 Antioxidant, Ferroptosis-Targeted, and Mitochondria-Targeted Therapies

Nrf2 pharmacological activators (sulforaphane, curcumin, bardoxolone methyl) provide targeted upstream antioxidant augmentation while simultaneously reducing NF-κB-mediated inflammation through reciprocal antagonism. Ferroptosis inhibitors (ferrostatin-1, liproxstatin-1) and GPX4 inducers (vitamin E, selenium) protect against iron-catalyzed lipid peroxidation-

driven cell death in metabolic and infectious organ injury. Mitochondria-targeted antioxidants (MitoQ, SS-31/elamipretide) address the root source of mtROS generation, preventing NLRP3 inflammasome activation and supporting mitochondrial biogenesis recovery through PGC-1α upregulation. Figure 4 presents the complete eight-domain therapeutic framework for restoring immunoendocrine and redox balance.

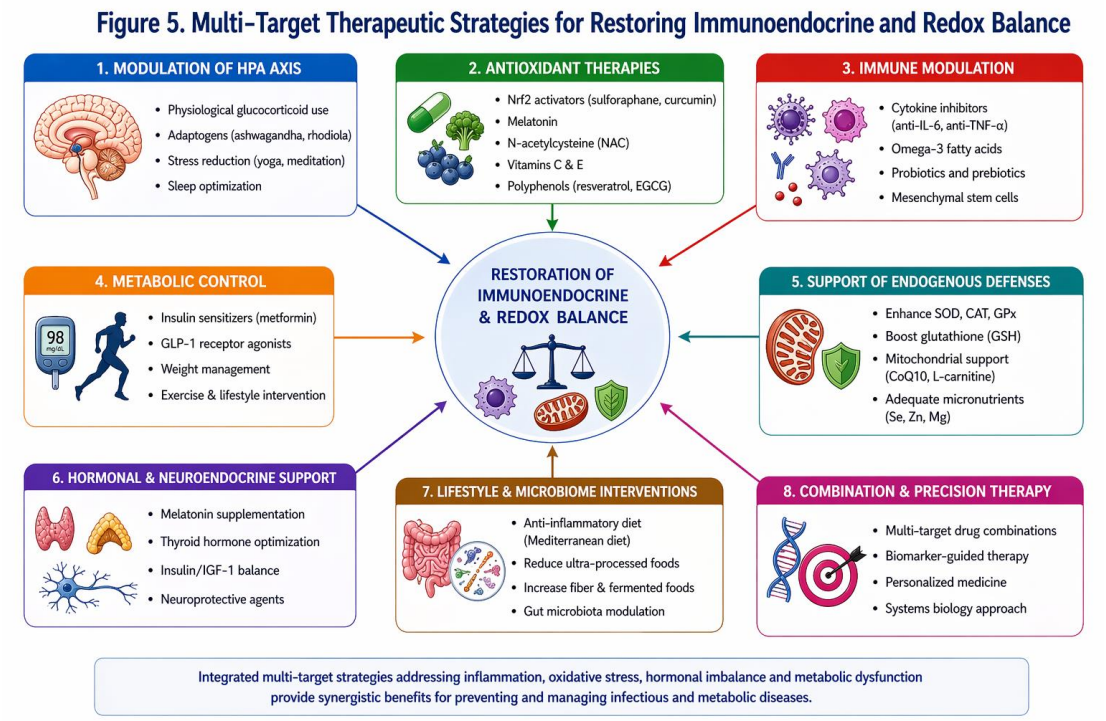

Figure 4. Multi-Target Therapeutic Strategies for Restoring Immunoendocrine and Redox Balance. Eight integrated therapeutic domains converge on restoring immunoendocrine and redox homeostasis: (1) HPA Axis Modulation — physiological glucocorticoid use, adaptogens (ashwagandha, rhodiola), stress reduction, sleep optimization; (2) Antioxidant Therapies — Nrf2 activators (sulforaphane, curcumin), melatonin, NAC, vitamins C and E, polyphenols (resveratrol, EGCG); (3) Immune Modulation — cytokine inhibitors (anti-IL-6, anti-TNF-α), omega-3 fatty acids, probiotics and prebiotics, mesenchymal stem cells; (4) Metabolic Control — insulin sensitizers (metformin), GLP-1 receptor agonists, weight management, exercise; (5) Support of Endogenous Defenses — SOD/CAT/GPx enhancement, GSH boosting, mitochondrial support (CoQ10, L-carnitine), micronutrients (Se, Zn, Mg, Vitamin D); (6) Hormonal and Neuroendocrine Support — melatonin, thyroid optimization, insulin/IGF-1 balance, neuroprotective agents; (7) Lifestyle and Microbiome Interventions — Mediterranean diet, fiber increase, gut microbiota modulation; (8) Combination and Precision Therapy — biomarker-guided multi-target drug combinations, personalized medicine, systems biology approach.

Table 3. Therapeutic Strategies Targeting Immunoendocrine, Oxidative Stress, Ferroptosis, and Mitochondrial Pathways

Therapeutic Strategy	Target Pathway	Disease Application	Evidence Level	Key Limitations
Low-dose hydrocortisone	HPA axis restoration (CIRCI)	Septic shock, Critical illness	RCT Level I (ADRENAL trial)	Risk of secondary immunosuppression
Vitamin C + E supplementation	Direct ROS scavenging	MetS, T2DM, Sepsis	Meta-analysis Level I	Variable bioavailability; dose-dependent
Melatonin supplementation	Nrf2 activation + ferroptosis inhibition	COVID-19, T2DM, Sepsis	RCT/Observational Level II	Dose optimization still required
N-acetylcysteine (NAC)	GSH precursor replenishment	Liver disease, Sepsis, ARDS	RCT Level I	GI intolerance at high intravenous doses
Metformin	AMPK activation; mROS suppression	T2DM, Metabolic syndrome	RCT Level I (multiple)	Contraindicated in renal impairment
Sulforaphane / DMF	Nrf2 pharmacological activation	Inflammatory + metabolic disorders	Phase II RCT / Pilot (Level III)	Long-term clinical safety unclear
Ferrostatin-1 / Liproxstatin-1	GPX4 rescue; ferroptosis inhibition	Ischemia, Liver injury, Sepsis	Pre-clinical Level IV	Not yet approved for human use
MitoQ / SS-31 (Elamipretide)	Mitochondria-targeted ROS scavenging	Heart failure, MetS, Sepsis	Phase II RCT (Level II)	High cost; limited clinical accessibility

Note. HPA = Hypothalamic-Pituitary-Adrenal; CIRCI = Critical illness-related corticosteroid insufficiency; ARDS = Acute Respiratory Distress Syndrome; MetS = Metabolic Syndrome; GSH = Glutathione; AMPK = AMP-activated protein kinase; DMF = Dimethyl fumarate; MitoQ = Mitoquinone mesylate; GI = Gastrointestinal.

Table 4. Identified Research Gaps and Proposed Future Investigations

Research Gap	Significance	Proposed Investigation	Priority Level
Sex-specific immunoendocrine differences in infection and MetS	Females exhibit distinct HPA kinetics and Nrf2 upregulation	Prospective sex-stratified longitudinal cohort studies	High
Long-COVID endocrine and oxidative sequelae	Persistent HPA hyporesponsiveness post-SARS-CoV-2	Multi-center prospective studies with ≥12-month follow-up	High
Ferroptosis biomarkers in clinical metabolic-infectious overlap	GPX4 suppression links T2DM and severe infection mortality	Prospective biobank studies with validated ferroptosis panels	High
Mitochondrial biogenesis dynamics during sepsis recovery	mtDNA damage persists weeks after clinical resolution	Longitudinal plasma mtDNA copy number monitoring (ICU cohorts)	Moderate–High
AI/ML predictive models integrating immunoendocrine-redox axes	No validated ML model simultaneously integrates all five axes	Deep learning models trained on multi-biomarker longitudinal datasets	Emerging – High

Note. HPA = Hypothalamic-Pituitary-Adrenal; GPX4 = Glutathione Peroxidase 4; mtDNA = Mitochondrial DNA; ICU = Intensive Care Unit; AI = Artificial Intelligence; ML = Machine Learning; MetS = Metabolic Syndrome.

Table 5. Molecular Pathways Linking Immunoendocrine Dysregulation, Oxidative Stress, and Cell Death: Summary and Therapeutic Targets

Molecular Pathway	Key Molecules	Biological Function	Disease Relevance	Therapeutic Target
Nrf2/Keap1	Nrf2, Keap1, HO-1, NQO1, GCL	Master antioxidant response regulator	MetS, Sepsis, T2DM, Parasitosis	Sulforaphane, DMF, bardoxolone
NF-κB	p65, p50, IκBα, IKKβ	Central pro-inflammatory transcription	All infectious + metabolic diseases	Corticosteroids, curcumin, NAC
AMPK/mTOR axis	AMPK, ACC, mTORC1, PGC-1α, S6K	Energy sensor; immunometabolic regulator	T2DM, Obesity, Sepsis	Metformin, rapamycin analogues
NLRP3 Inflammasome	NLRP3, ASC, Pro-caspase-1, IL-1β, IL-18	ROS/mtDNA-triggered innate immune activation	T2DM, COVID-19, Gout, Sepsis	MCC950, colchicine, melatonin
Ferroptosis pathway	GPX4, FSP1, ACSL4, System Xc^-, Ferritin	Iron-dependent lipid peroxidation cell death	NAFLD, T2DM, Sepsis, Ischemia	Ferrostatin-1, liproxstatin, Vit. E
HIF-1α / Warburg axis	HIF-1α, PKM2, LDHA, PHD1-3	Hypoxia-ROS sensing; immunometabolic reprogramming	Infection, Tumor microenvironment, Sepsis	PHD inhibitors; itaconate derivatives
Microbiome–HPA axis	SCFAs, butyrate, LPS, serotonin precursors	Gut-to-endocrine-immune signaling modulator	T2DM, COVID-19, Chronic infections	Probiotics, prebiotics, FMT

Note. Nrf2 = Nuclear factor erythroid 2-related factor 2; NF-κB = Nuclear Factor kappa B; AMPK = AMP-activated protein kinase; mTOR = mechanistic target of rapamycin; NLRP3 = NOD-like receptor protein 3; GPX4 = Glutathione Peroxidase 4; ACSL4 = Acyl-CoA Synthetase Long Chain Family Member 4; HIF-1α = Hypoxia-Inducible Factor-1 alpha; SCFAs = Short-Chain Fatty Acids; FMT = Fecal Microbiota Transplantation; DMF = Dimethyl fumarate.

12. Critical Discussion

The evidence reviewed herein supports a comprehensive model in which immunoendocrine dysregulation, oxidative stress, mitochondrial dysfunction, ferroptosis, and immunometabolic reprogramming constitute mutually reinforcing pathological drivers across infectious and metabolic diseases. Critical appraisal reveals important limitations: most mechanistic insights into ferroptosis and immunometabolism derive from experimental models requiring cautious extrapolation to human pathology. The temporal sequencing of interconnected pathways—which dysfunction precedes which—remains incompletely characterized in clinical studies.

Standardization of biomarker panels is urgently needed: validated ferroptosis markers (plasma GPX4 activity, 4-hydroxynonenal, acylcarnitine profiles), mitochondrial function indices (plasma mtDNA copy number, lactate/pyruvate ratios), and immunometabolic signatures (monocyte glycolytic index) would enable meaningful cross-study comparisons. Sex-based differences across all five pathophysiological axes are particularly

undercharacterized—females exhibit distinct HPA cortisol kinetics, estrogen-mediated Nrf2 upregulation, differential NLRP3 sensitivity, and sex-hormone-modulated gut microbiome composition compared to males, with profound implications for therapeutic response that current literature has inadequately resolved.

13. Future Perspectives

Multiomics integration—combining transcriptomics, metabolomics, lipidomics (critical for ferroptosis mapping), and proteomics—at single-cell resolution will enable comprehensive simultaneous characterization of all five pathophysiological axes. Artificial intelligence and deep learning applied to multi-dimensional biomarker datasets offer transformative capacity to identify personalized immunoendocrine-oxidative risk signatures, enabling precision therapeutic targeting. The microbiome-immunoendocrine-oxidative triad represents a high-priority research frontier: computational models linking microbiome compositional signatures to immunoendocrine hormonal profiles and systemic oxidative biomarkers could establish microbiome profiling as a standard component of disease workup. Sex-stratified randomized controlled trials with pre-specified mechanistic subgroup analyses are urgently needed to develop gender-informed therapeutic protocols for these highly prevalent, interconnected diseases.

14. Conclusion

Immunoendocrine interactions and oxidative stress constitute an integrated pathophysiological framework critically shaping disease progression across infectious and metabolic conditions. This review has substantially expanded the conventional model by incorporating mitochondrial dysfunction, ferroptosis, immunometabolic reprogramming, and the microbiome-endocrine-immune axis as equal-weight pathophysiological participants. The clinical evidence across COVID-19, T2DM, metabolic syndrome, and parasitic infections consistently demonstrates that these five axes operate as an integrated self-amplifying system.

Effective clinical management requires multi-target therapeutic strategies simultaneously addressing endocrine restoration, Nrf2-mediated antioxidant augmentation, ferroptosis inhibition, mitochondrial biogenesis support, and microbiome normalization—rather than the single-target approaches that have historically yielded disappointing clinical outcomes despite compelling mechanistic rationales. As the field advances toward multiomics integration, AI-driven precision medicine, and sex-stratified therapeutic protocols, the vision of comprehensive immunoendocrine-oxidative disease management moves progressively from mechanistic aspiration to clinical reality.

Declarations

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