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PSORIASIS AS A SYSTEMIC IMMUNOMETABOLIC DISORDER

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ABSTRACT
Psoriasis has traditionally been viewed as a chronic immune-mediated skin disease; however, emerging evidence reveals a complex systemic disorder involving immune, metabolic, gastrointestinal, and neuroendocrine dysfunction. This narrative review synthesizes current insights into the IL-23/Th17 axis, TNF-α and IL-6 signaling, adipokine imbalance, insulin resistance, gut dysbiosis, intestinal permeability, and hypothalamic–pituitary–adrenal (HPA) axis dysregulation. These interconnected pathways form a self-reinforcing inflammatory network that manifests in the skin but originates systemically. Understanding psoriasis as an immunometabolic disease highlights the need for integrated therapeutic strategies that address metabolic health, gut integrity, neuroendocrine balance, and immune modulation. This systems-biology perspective offers a foundation for future research and more comprehensive clinical management.

1. INTRODUCTION

Psoriasis has long been classified as a chronic, immune-mediated inflammatory skin disease characterized by hyperkeratosis, parakeratosis, and sharply demarcated erythematous plaques with silvery scale. Although traditionally viewed as a dermatologic condition, a growing body of evidence now positions psoriasis as a systemic inflammatory disorder with far-reaching metabolic, immunological, and neuroendocrine consequences. “The inflammatory burden in psoriasis extends beyond the skin… with heightened risks of cardiometabolic conditions, including atherosclerosis, insulin resistance, and non-alcoholic fatty liver disease.” This shift in understanding reflects a broader recognition that cutaneous inflammation is only one manifestation of a complex, multisystem disease process.

At the immunological core of psoriasis lies a dysregulated interplay between innate and adaptive immune pathways. The IL-23/Th17 axis, TNF-α signaling, and aberrant T-cell activation drive keratinocyte hyperproliferation and chronic inflammation. Yet emerging findings — including elevated IgE levels, mast-cell activation, and innate immune signatures — challenge the traditional Th1/Th17 paradigm and suggest a more heterogeneous immune landscape.

Parallel to these immune abnormalities, psoriasis is increasingly linked to metabolic dysfunction, particularly insulin resistance, visceral adiposity, and adipokine imbalance. “Omentin… is consistently found at reduced serum levels in individuals with psoriasis,” highlighting a potential immunometabolic bridge between skin inflammation and systemic disease.

Beyond immunity and metabolism, psoriasis intersects with gut physiology, neuroendocrine regulation, and mental health. Hypochlorhydria, dysbiosis, and increased intestinal permeability may amplify systemic inflammation, while cytokine-mediated neuroimmune activation contributes to the disproportionately high prevalence of depression in psoriatic patients. This aligns with your observation that “cytokines cross the blood–brain barrier, influencing neurotransmitter balance and neuroinflammation.”

Taken together, these findings support a unified systems-biology model in which immune, metabolic, gastrointestinal, and neuroendocrine pathways converge to shape the clinical expression of psoriasis. This narrative review synthesizes these interconnected mechanisms, reframing psoriasis as a systemic immunometabolic disorder and highlighting implications for integrated clinical management and future research.

2. IMMUNOPATHOGENESIS OF PSORIASIS

Psoriasis is driven by a complex interplay between innate and adaptive immune pathways, resulting in chronic cutaneous and systemic inflammation. Although historically framed as a predominantly T-cell–mediated disorder, contemporary research reveals a far more intricate immunological landscape involving cytokine networks, dendritic cell activation, mast-cell signaling, and innate immune dysregulation. This section synthesizes these mechanisms to illustrate how immune dysfunction extends beyond the skin and contributes to the systemic nature of psoriatic disease.

2.1 The IL-23/Th17 Axis: The Central Driver of Psoriatic Inflammation

The IL-23/Th17 pathway is widely recognized as the immunological backbone of psoriasis. IL-23, produced by dendritic cells and macrophages, promotes the expansion and stabilization of Th17 cells, which secrete IL-17A, IL-17F, and IL-22 — cytokines that directly induce keratinocyte hyperproliferation and aberrant differentiation.

Keratinocytes, in turn, release antimicrobial peptides (e.g., LL-37), chemokines, and pro-inflammatory mediators that perpetuate a self-amplifying inflammatory loop. “A dynamic interplay between innate and adaptive immune responses” highlights why IL-17 and IL-23 inhibitors have transformed psoriasis therapy.

2.2 TNF-α and IL-6: Master Regulators of Systemic Inflammation

TNF-α and IL-6 are pivotal cytokines linking cutaneous inflammation to systemic disease. TNF-α promotes dendritic cell maturation, T-cell activation, and endothelial dysfunction. At the same time, IL-6 drives acute-phase responses and

contributes to metabolic disturbances. “Elevated levels of these markers are common in psoriasis patients,” and this is clinically validated by the normalization of TNF-α and IL-6 levels following effective therapy, where “serum TNF-α and IL-6 levels normalized” alongside PASI improvement.
These cytokines also contribute to:
• Atherosclerosis
• Insulin resistance
• Hepatic inflammation
• Neuroinflammation
reinforcing the systemic nature of psoriatic disease.

2.3 T-Cell Dysregulation and Keratinocyte Crosstalk
Psoriasis is characterized by aberrant activation of CD4+ and CD8+ T cells. “These T cells become overactive and mistakenly attack healthy skin cells,” triggering cytokine release and rapid keratinocyte turnover.
Key features include:
• CD8+ T cells infiltrating the epidermis
• CD4+ Th1 and Th17 cells dominating the dermis
• IFN-γ and IL-17 synergistically amplifying inflammation

2.4 Innate Immunity and Autoinflammation: Beyond the Adaptive Paradigm
While chronic plaque psoriasis is largely adaptive-immune-driven, generalized pustular psoriasis (GPP) exhibits features of autoinflammation. “Generalized pustular psoriasis displays features of autoinflammation, highlighting the role of innate immunity and neutrophilic activation.”
Innate immune contributors include:
• Neutrophils (forming Munro microabscesses)
• IL-36 pathway activation
• Mast-cell degranulation
• Complement activation
    - Keratinocytes acting as active immune participants, not passive targets
    - This bidirectional communication between immune cells and keratinocytes sustains chronic plaque formation.

2.5 IgE and Mast-Cell Activation: Expanding the Immunological Landscape
: The emerging role of IgE in psoriasis. “Elevated serum IgE levels challenge the historical distinction between Th1/Th17-driven autoimmune responses and Th2-mediated hypersensitivity reactions.”
This is a paradigm-shifting observation.
Elevated IgE in psoriasis may reflect:
• Mast-cell activation
• Skin barrier dysfunction
• Overlap with atopic pathways
• Systemic immune dysregulation
Mast cells release TNF-α, IL-6, and histamine — all of which can exacerbate keratinocyte proliferation and systemic inflammation. This positions IgE as a potential biomarker for disease severity and a bridge between psoriatic and atopic inflammation.

2.6 Cytokine Networks and Systemic Spillover
Psoriasis is not confined to the skin because its cytokines are not confined to the skin.
IL-17, IL-6, TNF-α, and IFN-γ enter systemic circulation, contributing to:
• Endothelial dysfunction
• Insulin resistance
• Hepatic steatosis
• Neuroinflammation
• Depression
“Circulating factors indicative of systemic inflammation and endothelial activation have been detected.”
This systemic cytokine spillover is the mechanistic foundation for the multisystem comorbidities seen in psoriatic disease.

3. METABOLIC DYSFUNCTION AND INSULIN RESISTANCE IN PSORIASIS
Metabolic dysfunction is increasingly recognized as a central component of psoriatic disease. Beyond its cutaneous manifestations, psoriasis is strongly associated with insulin resistance (IR), visceral adiposity, dyslipidaemia, and an elevated risk of cardiometabolic disorders. These associations are not merely epidemiological; they reflect shared inflammatory pathways and bidirectional interactions between immune activation and metabolic imbalance. “Insulin resistance has been identified as a significant contributor to the epidermal changes observed in psoriasis, including keratinocyte hyperproliferation and abnormal differentiation.”

3.1 Insulin Resistance as a Driver of Keratinocyte Dysfunction

Insulin resistance is highly prevalent in individuals with psoriasis, even in those without overt diabetes. Hyperinsulinemia — a compensatory response to IR — exerts proliferative effects on keratinocytes, contributing to hallmark psoriatic features such as:

- Accelerated epidermal turnover
- Impaired differentiation
- Increased inflammatory signalling

"Insulin resistance… contributes to the epidermal changes observed in psoriasis." Mechanistically, insulin and IGF-1 receptors on keratinocytes activate PI3K/Akt and MAPK pathways, promoting hyperproliferation and reducing apoptosis. This creates a metabolic environment that amplifies cutaneous inflammation.

3.2 Adipokine Imbalance: Omentin, Visfatin, and Resistin

Adipose tissue is an active endocrine organ, and its secreted adipokines play a crucial role in systemic inflammation. Psoriasis is characterized by a distinct adipokine profile:

Omentin

"Omentin… is consistently found at reduced serum levels in individuals with psoriasis."

Omentin enhances insulin sensitivity and exerts anti-inflammatory effects. Reduced levels correlate with:

- Higher BMI
- Increased waist circumference
- Greater disease severity

This suggests that omentin deficiency may be a mechanistic link between visceral adiposity and psoriatic inflammation

Visfatin and Resistin

Psoriatic patients often exhibit elevated Visfatin and resistin, both of which:

- Promote TNF-α and IL-6 production
- Impair insulin signalling
- Contribute to endothelial dysfunction

This adipokine imbalance reinforces the systemic inflammatory state characteristic of psoriatic disease.

3.3 TNF-α, IL-6, and the Immunometabolic Loop

TNF-α and IL-6 — central cytokines in psoriasis — are also key mediators of insulin resistance. TNF-α impairs insulin receptor signalling by promoting serine phosphorylation of IRS-1, while IL-6 induces hepatic gluconeogenesis and disrupts adipocyte metabolism.

"TNF-α stands out as a pivotal molecule influencing both insulin signalling and psoriatic pathogenesis."

This creates a self-reinforcing loop:

1. Psoriatic inflammation increases TNF-α and IL-6
2. These cytokines worsen insulin resistance
3. Insulin resistance increases keratinocyte proliferation and systemic inflammation
4. Worsening inflammation further elevates TNF-α and IL-6

This loop explains why metabolic syndrome is disproportionately common in psoriasis and why anti-TNF therapies often improve insulin sensitivity.

3.4 IgE, Mast Cells, and Metabolic Inflammation

A novel connection between IgE-mediated immune activation and insulin resistance.

"IgE binds to mast cells, which release pro-inflammatory cytokines like TNF-α and IL-6—both known to impair insulin signalling."

This positions IgE as a potential mediator of metabolic dysfunction in psoriasis. Mast-cell–derived cytokines contribute to:

- Adipose tissue inflammation
- Impaired glucose uptake
- Increased visceral fat deposition

Emerging evidence suggests sex-specific effects, with premenopausal women showing stronger associations between elevated IgE and IR.

3.5 Hyperinsulinemia, Hypochlorhydria, and Gastrointestinal Consequences

"Chronic hyperinsulinemia has been associated with hypochlorhydria."

Reduced gastric acid secretion contributes to:

- Impaired protein digestion
- Nutrient deficiencies (iron, B12, zinc)
- Dysbiosis
- Increased intestinal permeability

These gastrointestinal changes amplify systemic inflammation and may worsen psoriatic disease. This connection forms a bridge to the next section on the gut–skin axis.

4. THE GASTROINTESTINAL AXIS: HYPOCHLORHYDRIA, DYSBIOSIS, AND INTESTINAL PERMEABILITY

The gastrointestinal (GI) system plays a pivotal role in shaping systemic immunity, metabolic homeostasis, and inflammatory tone. Psoriasis has been increasingly linked to alterations in gastric function, microbial composition, and intestinal barrier integrity. "Hypochlorhydria… fosters gut dysbiosis and compromises the intestinal barrier, leading to leaky gut syndrome." These interconnected disturbances form a mechanistic bridge between metabolic dysfunction, immune activation, and cutaneous inflammation.

Gastric acid secretion, microbial ecology, and intestinal permeability contribute to systemic inflammation and disease severity.

4.1 Hypochlorhydria: A Metabolic and Immunological Catalyst

Hypochlorhydria — reduced gastric acid secretion — is increasingly recognized as a contributor to systemic inflammation. "Chronic hyperinsulinemia has been associated with hypochlorhydria," positioning gastric dysfunction as a downstream effect of metabolic imbalance.

Low gastric acid impairs:

- Protein digestion, leading to antigenic load and immune activation
- Absorption of key nutrients (iron, B12, zinc, calcium)
- Sterilization of ingested pathogens, increasing microbial overgrowth
- Activation of digestive enzymes, reducing nutrient assimilation

These changes create a permissive environment for dysbiosis and immune dysregulation. In psoriasis, where insulin resistance and systemic inflammation are already present, hypochlorhydria may amplify disease severity by increasing antigen exposure and altering gut microbial composition.

4.2 Dysbiosis: Altered Microbial Ecology in Psoriatic Disease

"Gut dysbiosis… contributes to the development or exacerbation of autoimmune conditions, including psoriasis." This aligns with emerging research showing that psoriatic patients exhibit:

- Reduced microbial diversity
- Lower levels of beneficial SCFA-producing bacteria (e.g., Faecalibacterium, Roseburia)
- Increased pro-inflammatory species
- Altered Firmicutes/Bacteroidetes ratios

Dysbiosis promotes systemic inflammation through:

- Increased production of lipopolysaccharides (LPS)
- Reduced short-chain fatty acids (SCFAs), especially butyrate
- Impaired regulatory T-cell (Treg) induction
- Enhanced Th17 polarization

"The number of butyrate-producing bacteria and faecal butyrate levels increased… as did the proliferation of CD4+ Foxp3+ regulatory T cells." This underscores the therapeutic potential of restoring microbial balance.

4.3 Intestinal Permeability: The "Leaky Gut" Contribution to Systemic Inflammation

Increased intestinal permeability — colloquially termed "leaky gut" — allows microbial fragments, toxins, and undigested food particles to translocate into systemic circulation. "Triggers a chronic immune response… characterized by elevated pro-inflammatory cytokines and aberrant T-cell signalling."

Mechanistically, permeability is driven by:

- Zonulin activation
- Tight junction disruption
- Dysbiosis-induced inflammation
- Nutrient deficiencies (zinc, B vitamins)
- Hypochlorhydria

Once the barrier is compromised, circulating microbial products activate:

- Toll-like receptors (TLRs)
- Dendritic cells
- Mast cells
- Th17 pathways

This systemic immune activation contributes directly to psoriatic inflammation and may explain why even patients with mild skin disease exhibit elevated inflammatory markers.

4.4 The Gut–Skin Axis: Bidirectional Communication

"The skin should not be considered as an isolated organ but rather as a functioning system that communicates with the internal environment."

The gut–skin axis operates through:

Immune Pathways

- Cytokines (IL-6, TNF-α, IL-17)
- T-cell trafficking
- Mast-cell activation

Metabolic Pathways
• SCFA production
• Bile acid metabolism
• Insulin sensitivity
Microbial Metabolites
• Histamine
• Indoles
• Butyrate
Histamine is particularly relevant. “Histamine… plays a major role in triggering allergic and inflammatory reactions.” Elevated histamine from dysbiosis or diet can worsen psoriatic inflammation.

4.5 The Gut–Brain–Skin Axis: Neuroimmune Integration
“Chronic intestinal inflammation… leads to systemic release of cytokines that cross the blood–brain barrier, influencing neurotransmitter balance and neuroinflammation.”
This triad operates through:
• Cytokine signaling (IL-6, TNF-α, IL-17)
• Vagal nerve pathways
• Microbial neurotransmitter production (GABA, serotonin precursors)
• HPA axis modulation
This explains why:
• Depression is disproportionately common in psoriasis
• Stress exacerbates skin inflammation
• Gut-directed therapies can improve mood and skin symptoms

5. NEUROENDOCRINE AND HPA AXIS DYSREGULATION IN PSORIATIC DISEASE
Psoriasis is increasingly recognized as a disorder that extends beyond immune and metabolic dysfunction to involve profound neuroendocrine disturbances. Chronic inflammation, metabolic stress, and gut dysbiosis converge on the hypothalamic–pituitary–adrenal (HPA) axis, altering cortisol dynamics and contributing to both cutaneous and psychological manifestations of the disease. “Persistent hyperinsulinemia, gut inflammation, and neuroimmune activation can dysregulate the HPA axis, leading to either adrenal hyperactivity or fatigue.” Neuroendocrine imbalance amplifies psoriatic inflammation and contributes to the high burden of depression, fatigue, and stress reactivity observed in psoriatic patients.

5.1 The HPA Axis: A Central Regulator of Stress and Immunity
The HPA axis orchestrates the body’s response to stress through a tightly regulated cascade:
1. Hypothalamus releases corticotropin-releasing hormone (CRH)
2. Pituitary gland secretes adrenocorticotropic hormone (ACTH)
3. The adrenal cortex produces cortisol
Cortisol exerts anti-inflammatory effects by suppressing NF-κB activation, inhibiting pro-inflammatory cytokines, and modulating T-cell responses. In healthy physiology, this system maintains immune balance.
However, in psoriasis, chronic inflammation and metabolic stress disrupt this regulatory loop.

5.2 Chronic Inflammation and Cortisol Dysregulation
The prolonged inflammatory and metabolic stress can lead to “hypocortisolism, which diminishes the body’s ability to regulate immune responses
Two patterns are commonly observed:
1. Early Hypercortisolism
• Elevated cortisol in response to acute inflammation
• Temporary suppression of immune activity
• Increased anxiety, agitation, and sleep disruption
2. Late Hypocortisolism (Adrenal Fatigue Pattern)
• Reduced cortisol output despite ongoing inflammation
• Impaired suppression of IL-6, TNF-α, and IL-17
• Increased fatigue, depression, and pain sensitivity
This transition from hyper- to hypo-cortisolism reflects HPA axis exhaustion and contributes to the chronicity of psoriatic inflammation.

5.3 Cytokine-Driven Neuroinflammation
Pro-inflammatory cytokines central to psoriasis — including IL-6, TNF-α, and IL-17 — can cross the blood–brain barrier or signal through neural pathways. “These cytokines… cross the blood–brain barrier, influencing neurotransmitter balance and neuroinflammation.”
Cytokine-mediated neuroinflammation affects:
• Serotonin synthesis (via tryptophan depletion)
• Dopamine signalling (reducing motivation and reward)

• Glutamate excitotoxicity (increasing anxiety and cognitive fog)
• Microglial activation (sustaining neuroinflammation)
These mechanisms explain why depression, cognitive dysfunction, and fatigue are disproportionately common in psoriasis.

5.4 The Stress–Inflammation Loop
Psychological stress is a well-known trigger for psoriatic flares. This reflects a bidirectional loop:
1. Stress activates the HPA axis
2. Cortisol initially suppresses inflammation
3. Chronic stress leads to cortisol resistance or depletion
4. Inflammation increases
5. Worsening skin symptoms increase psychological stress

"This adrenal imbalance exacerbates skin inflammation by failing to counteract pro-inflammatory cytokines."
This loop is further amplified by:
• Sleep disruption
• Insulin resistance
• Gut dysbiosis
• Chronic pain
Together, these factors create a self-perpetuating cycle of neuroimmune activation.

5.5 The Gut–Brain–Skin Axis: A Neuroendocrine Bridge
"Gut inflammation… leads to systemic release of cytokines that cross the blood–brain barrier, influencing neurotransmitter balance and neuroinflammation."
The gut–brain–skin axis operates through:
Neural Pathways
• Vagus nerve signaling
• Enteric nervous system activation
Endocrine Pathways
• Cortisol
• Serotonin (90% produced in the gut)
• Melatonin
Immune Pathways
• Cytokine trafficking
• Mast-cell activation
• T-cell priming
This integrated network explains why interventions targeting gut health can improve both mood and skin symptoms.

5.6 Depression and Psoriasis: A Shared Inflammatory Biology
Depression in psoriasis is not merely a psychological reaction to visible skin lesions. It is a biological consequence of systemic inflammation and HPA axis dysregulation.
Key shared mechanisms include:
• Elevated IL-6 and TNF-α
• Reduced cortisol responsiveness
• Altered serotonin and dopamine signalling
• Microglial activation
• Increased intestinal permeability
Patients with mild psoriasis may exhibit "subclinical gut inflammation and elevated markers of intestinal permeability," which can drive neuroinflammation and mood disturbances.
This reframes depression in psoriasis as an inflammatory neuroendocrine disorder, not a secondary comorbidity.

6. AN INTEGRATED SYSTEMS MODEL OF PSORIASIS
Psoriasis is best understood not as an isolated dermatologic condition but as a multisystem disorder arising from the convergence of immune, metabolic, gastrointestinal, and neuroendocrine dysfunction. Each of these domains has been traditionally studied in isolation; however, emerging evidence demonstrates that these systems interact dynamically, forming a self-reinforcing network of chronic inflammation. This integrated model reframes psoriasis as a systemic immunometabolic disease with cutaneous manifestations rather than a skin-limited pathology.

6.1 The Immune–Metabolic Interface: A Bidirectional Amplifier
The immune and metabolic systems are deeply intertwined. Pro-inflammatory cytokines central to psoriasis — including TNF-α, IL-6, and IL-17 — impair insulin signalling, promote hepatic gluconeogenesis, and disrupt adipocyte function. Conversely, metabolic dysfunction, particularly insulin resistance and visceral adiposity, fuels immune activation through adipokine imbalance and chronic low-grade inflammation.
"TNF-α stands out as a pivotal molecule influencing both insulin signaling and psoriatic pathogenesis."
This creates a bidirectional loop:

• Immune activation worsens metabolic dysfunction
• Metabolic dysfunction amplifies immune activation
This loop explains why psoriasis is strongly associated with obesity, metabolic syndrome, and cardiovascular disease — and why metabolic interventions often improve skin outcomes.

6.2 The Gut–Immune Axis: A Source of Systemic Inflammatory Load
The gastrointestinal system acts as a major regulator of immune tone. Hypochlorhydria, dysbiosis, and increased intestinal permeability contribute to systemic immune activation by increasing antigen exposure and microbial translocation.

Key mechanisms include:
• Dysbiosis reduces SCFA-producing bacteria, impairing Treg induction
• Leaky gut allows LPS and microbial fragments into circulation
• Histamine-producing bacteria amplify mast-cell activation
• Nutrient malabsorption (zinc, B12, iron) weakens epithelial and immune integrity
"Even patients with mild psoriasis exhibit subclinical inflammation in the small intestine and increased intestinal permeability." This positions the gut as a primary driver of systemic inflammation rather than a secondary consequence.

6.3 The Neuroendocrine Axis: Stress, Cytokines, and Cortisol Dysregulation
The HPA axis integrates psychological stress with immune and metabolic responses. Chronic inflammation blunts cortisol responsiveness, while persistent stress disrupts immune regulation."Adrenal imbalance… failing to counteract pro-inflammatory cytokines."
This creates another reinforcing loop:
• Stress increases cytokine production
• Cytokines disrupt neurotransmitter balance
• Neuroinflammation worsens mood and sleep
• Poor sleep and depression increase systemic inflammation
• Inflammation worsens psoriasis
This neuroimmune loop explains why depression, anxiety, and fatigue are not merely comorbidities but core components of psoriatic disease biology.

6.4 The Skin as a Mirror of Systemic Dysfunction
"The skin should not be considered as an isolated organ but rather as a functioning system that communicates with the internal environment."
Keratinocytes are active immune participants. They respond to:
• Cytokines from systemic inflammation
• Microbial metabolites from the gut
• Hormonal signals from the HPA axis
• Metabolic cues such as insulin and IGF-1
Thus, psoriatic plaques represent the visible endpoint of a multisystem inflammatory cascade.

6.5 A Unified Systems Model of Psoriasis
Bringing these domains together, psoriasis emerges as a disease sustained by four interconnected hubs:
1. Immune Hub
Th17 activation, TNF-α, IL-6, IL-23, mast-cell signaling, and IgE involvement.
2. Metabolic Hub
Insulin resistance, adipokine imbalance, visceral adiposity, and hyperinsulinemia.
3. Gastrointestinal Hub
Hypochlorhydria, dysbiosis, leaky gut, and microbiome changes

metabolites.
4. Neuroendocrine Hub
HPA axis dysregulation, cortisol imbalance, cytokine-driven neuroinflammation.
These hubs interact through shared mediators:
• TNF-α and IL-6
• SCFAs and microbial metabolites
• Cortisol and stress hormones
• Insulin and IGF-1
• Mast-cell activation and histamine
The result is a self-perpetuating inflammatory network that manifests in the skin but originates systemically.

6.6 Clinical Implications of the Systems Model
This integrated framework has profound implications:
• Psoriasis should be screened as a multisystem disease, not a skin disorder
• Metabolic and gastrointestinal assessments are essential

• Psychological and neuroendocrine health must be addressed
• Therapies targeting a single pathway may be insufficient
• Immunometabolic and gut-directed interventions hold promise
Metabolic screening, gut health, and neuroimmune balance align perfectly with this systems-biology approach.
6.7 Summary: Psoriasis as a Systemic Immunometabolic Disorder
This integrated model reframes psoriasis as:
• Immune-driven
• Metabolically amplified
• Gut-mediated
• Neuroendocrine-modulated
This holistic understanding provides a foundation for the future of psoriatic disease management — one that moves beyond symptom suppression toward systemic restoration.

7. FUTURE DIRECTIONS AND THERAPEUTIC HORIZONS

The systems-biology model of psoriasis outlined in this review highlights the need for a paradigm shift in both research and clinical practice. Psoriasis is not merely a cutaneous disorder but a multisystem immunometabolic disease involving immune dysregulation, metabolic dysfunction, gastrointestinal imbalance, and neuroendocrine stress responses. This expanded understanding opens new avenues for biomarker discovery, therapeutic innovation, and integrative management strategies.

7.1 Biomarker Development: Toward Precision Immunometabolic Profiling

Immunological panel, noting markers such as IL-6, IL-17A, IL-23, TNF-α, IgE, CRP, complement proteins, and T-cell ratios. These biomarkers represent promising tools for:
• Disease stratification (e.g., Th17-dominant vs. IgE-dominant phenotypes)
• Predicting treatment response
• Monitoring systemic inflammation
• Identifying metabolic risk
Emerging candidates include:
• Adipokines (omentin, visfatin, resistin)
• Galectin-3
• Microbial metabolites (SCFAs, histamine, indoles)
• Markers of intestinal permeability (zonulin, LPS-binding protein)
Future research should focus on developing multidimensional biomarker panels that integrate immune, metabolic, and gut-derived signals to guide personalized therapy.

7.2 Immunometabolic Therapies: Targeting the Inflammatory–Metabolic Loop

Biologic therapies targeting IL-17, IL-23, and TNF-α have revolutionized psoriasis care, yet they do not address the underlying metabolic dysfunction that sustains systemic inflammation.

Promising metabolic interventions:
• **GLP-1 agonists** (e.g., bitter hop extract) for appetite regulation and insulin sensitivity
• **Micronutrients** such as magnesium, chromium, zinc, and biotin
• **Berberine** as an insulin-sensitizing agent
Future clinical trials should evaluate:
• GLP-1 agonists as adjunctive therapy in psoriasis
• Metabolic correction as a strategy to enhance biologic response
• Whether improving insulin sensitivity reduces IL-17 and TNF-α levels
This represents a major frontier in psoriasis research: treating the **metabolic engine that drives inflammation**.

7.3 Gut-Targeted Interventions: Restoring Microbial and Barrier Integrity

Strong evidence for the role of hypochlorhydria, dysbiosis, and intestinal permeability in psoriatic disease. This opens the door to gut-directed therapies such as:
1. Microbiome Restoration
• Probiotics
• Prebiotics
• SCFA-enhancing dietary fibers
• Fecal microbiota transplantation (future research)
2. Digestive Support
• Betaine HCl (to correct hypochlorhydria)
• Zinc carnosine (for mucosal repair)
• B-complex vitamins (for epithelial integrity)
3. Anti-Inflammatory Nutraceuticals
Your document highlights several promising agents:
• **Quercetin** (reduces IL-6, IL-17, TNF-α; improves microbiota)

• **Liposomal curcumin** (NF-κB suppression; regulatory immune effects)
• **Modified Citrus Pectin** (galectin-3 inhibition, immune modulation)
• **Omega-3 fatty acids** (SCFA enhancement; NF-κB inhibition)
• **Resveratrol** (TLR-4 downregulation; anti-inflammatory effects)
These compounds warrant rigorous clinical evaluation as adjunctive therapies.

7.4 Neuroendocrine Modulation: Addressing Stress Biology and HPA Axis Dysfunction
Given the strong evidence linking psoriasis to HPA axis dysregulation, future research should explore:
• Cortisol-modulating interventions
• Mind–body therapies (meditation, breathwork, vagal stimulation)
• Sleep optimization strategies
• Anti-inflammatory psychiatric treatments
"Neuroimmune activation contributes to mood disturbances, fatigue, and cognitive dysfunction," underscores the need for integrated dermatology-psychiatry research.

7.5 Lifestyle and Dietary Interventions: A Systems-Level Approach
Several dietary strategies that align with emerging evidence:
• **Anti-inflammatory diets** (rich in omega-3s, polyphenols, antioxidants)
• **High-fiber diets** to support SCFA production
• **Gluten-free/casein**-free trials in select patients
• **Reduction** of sugar, refined carbohydrates, and saturated fats
• **Avoidance of histamine-rich** or histamine-liberating foods
Future studies should evaluate:
• Diet–microbiome–immune interactions
• Personalized nutrition based on metabolic and microbial profiling
• Whether dietary interventions can reduce biologic dosing requirements

7.6 Integrative, Multidisciplinary Care Models
The systems model of psoriasis calls for a new clinical paradigm that integrates:
• Dermatology
• Endocrinology
• Gastroenterology
• Psychiatry
• Nutrition science
Such models could improve outcomes by addressing the root causes of systemic inflammation rather than focusing solely on cutaneous symptoms.

7.7 Summary: A New Horizon for Psoriatic Disease Research
Future research should prioritize:
• Immunometabolic biomarkers
• Gut-targeted therapies
• Neuroendocrine modulation
• Personalized nutrition
• Integrated care pathways
"These findings underscore the importance of metabolic screening in patients with psoriasis and advocate for an integrated management strategy that targets both immunological and metabolic pathways."
This systems-biology perspective represents the next frontier in psoriasis research and clinical practice.

8. CONCLUSION
Psoriasis has long been recognized as a chronic inflammatory skin disease, yet the evidence synthesized in this review proves that its biological footprint extends far beyond the epidermis. Psoriasis is a systemic immunometabolic disorder, shaped by the dynamic interplay of immune activation, metabolic dysfunction, gastrointestinal imbalance, and neuroendocrine stress responses. In this context, the skin becomes a visible marker of deeper physiological disturbances rather than the primary site of disease.
The immunopathogenesis of psoriasis is anchored in the IL-23/Th17 axis, TNF-α signaling, and T-cell dysregulation, but these pathways do not operate in isolation. They intersect with metabolic abnormalities such as insulin resistance, adipokine imbalance, and visceral adiposity — forming a bidirectional loop in which inflammation drives metabolic dysfunction and metabolic dysfunction amplifies inflammation. Reductions in protective adipokines like omentin and elevations in inflammatory mediators such as TNF-α and IL-6 underscore this immunometabolic convergence.

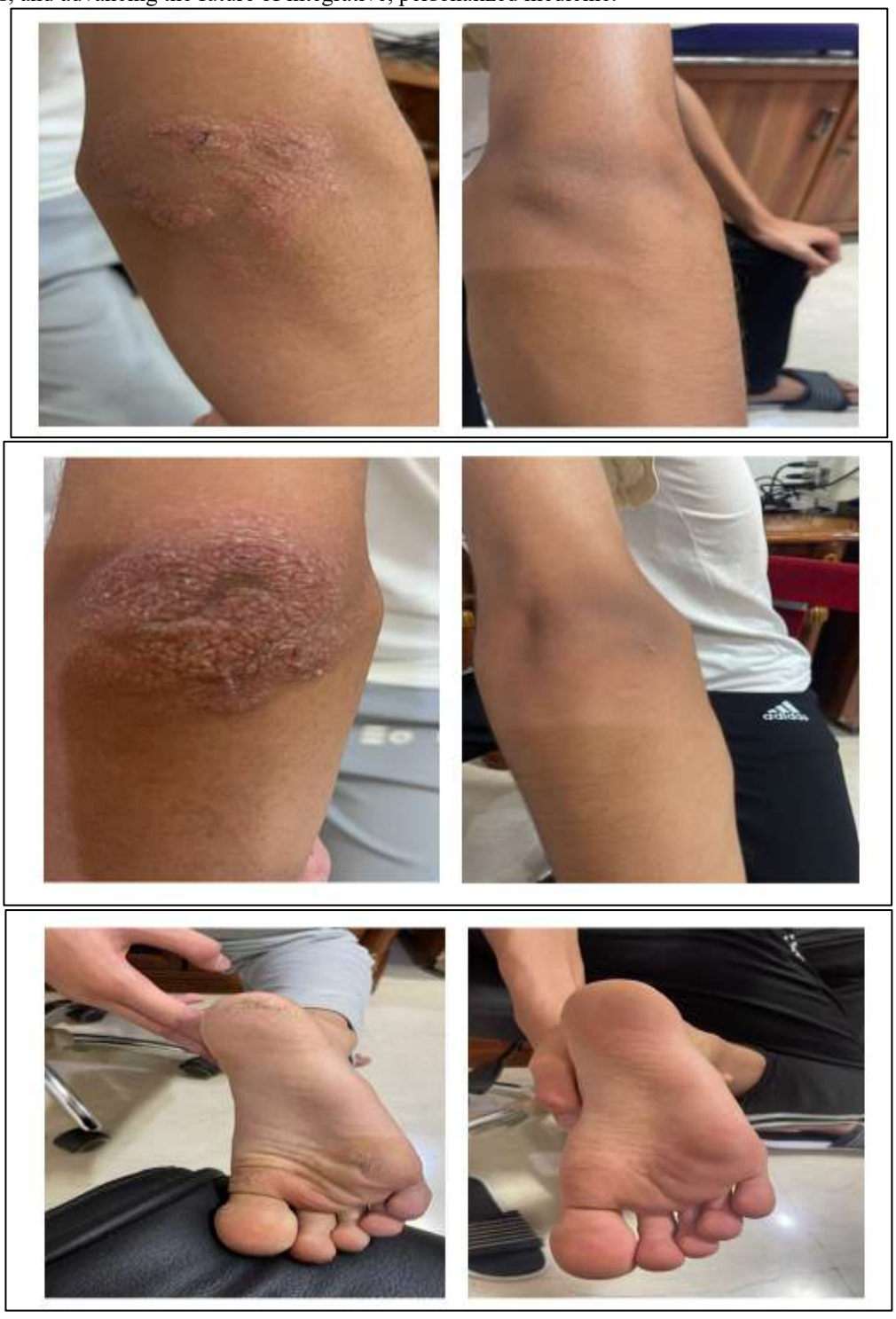
Gastrointestinal physiology further contributes to systemic inflammatory load. Hypochlorhydria, dysbiosis, and increased intestinal permeability create a permissive environment for microbial translocation and immune activation. These gut-derived signals interact with neuroendocrine pathways, particularly the HPA axis, where chronic inflammation and

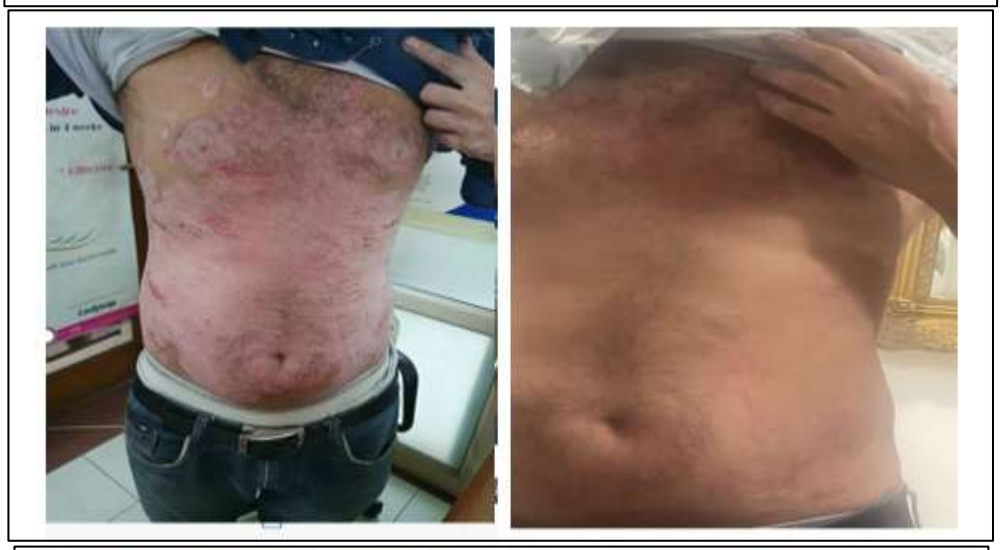
stress lead to cortisol dysregulation, neuroinflammation, and mood disturbances. This gut–brain–skin axis reframes depression and fatigue not as secondary comorbidities but as integral components of psoriatic disease biology.

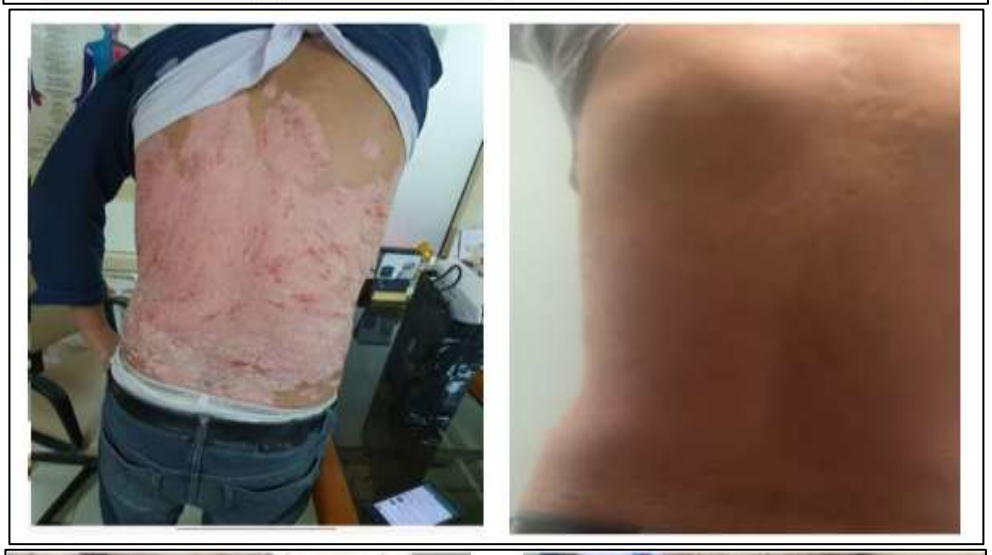
Taken together, these interconnected systems form a self-reinforcing inflammatory network that manifests in the skin but originates systemically. This integrated model challenges the traditional organ-specific view of psoriasis and calls for a more holistic, multidisciplinary approach to research and clinical care. Future therapeutic strategies must move beyond targeting isolated cytokines to address metabolic health, gut integrity, neuroendocrine balance, and lifestyle factors that shape systemic inflammation.

"The skin should not be considered as an isolated organ but rather as a functioning system that communicates with the internal environment," captures the essence of this paradigm shift. By embracing a systems-biology perspective, clinicians and researchers can better understand the complexity of psoriatic disease and develop interventions that restore balance across the interconnected networks that sustain health.

Psoriasis, therefore, is not simply a dermatologic condition — it is a window into the broader physiology of chronic inflammation. Recognizing and treating it as such offers the greatest promise for improving outcomes, reducing comorbidities, and advancing the future of integrative, personalized medicine.







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