Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 01 July 2026
Revised 20 Aug 2026
Accepted 03 Sep 2026

Natural Resources for Human Health 2026, Vol. 6 (19s): 1132–1139

KEYWORDS:
NF-κB, JAK-STAT, insulin resistance, pediatric inflammation, SOCS3, HOMA-IR, targeted therapy, Karachi.

NF-ΚB/JAK-STAT Signaling in Pediatric Metabolic and Inflammatory Disorders: Molecular Mechanisms Linking Chronic Inflammation to Insulin Resistance and Emerging Targeted Therapeutic Strategies

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ABSTRACT:

Background: Chronic low-grade inflammation driven by the Nuclear Factor kappa-B (NF-κB) and Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathways is increasingly recognized as a molecular bridge linking pediatric inflammatory disorders to insulin resistance (IR). However, quantitative evidence from South Asian pediatric cohorts remains scarce. This study aimed to investigate the molecular mechanisms connecting NF-κB/JAK-STAT signaling to IR in pediatric patients with chronic inflammatory and metabolic disorders and to evaluate the implications for emerging targeted therapies.

Methods: A prospective, cross-sectional analytical study was conducted across three tertiary care hospitals in Karachi, Pakistan (January 2025–August 2026). The cohort comprised 400 pediatric patients (aged 5–18 years) diagnosed with juvenile idiopathic arthritis (JIA, n=145), pediatric inflammatory bowel disease (pIBD, n=110), or primary obesity with IR (n=145). Fasting serum levels of NF-κB (p65), JAK2, STAT3, and SOCS3 were quantified via ELISA. IR was assessed using HOMA-IR. Data normalization via log-

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eISSN: 2583-1194

transformation was applied to skewed biomarker distributions. Statistical analyses included Pearson's correlation and multiple linear regression.

Results: Overall, 67.0% of the cohort exhibited elevated HOMA-IR (>2.5), with the highest prevalence in the obesity subgroup (76.6%) and adolescents aged 15–18 years (81.0%). Age-stratified analysis revealed a progressive, significant increase in NF-κB, JAK2, STAT3, and HOMA-IR from childhood to adolescence ($p<0.001$). Strong positive correlations were observed between SOCS3 and HOMA-IR ($r=0.65$, $p<0.001$) and NF-κB and HOMA-IR ($r=0.62$, $p<0.001$). Multiple linear regression identified log(SOCS3) (standardized $\beta=0.31$, $p<0.001$) and log(NF-κB) (standardized $\beta=0.28$, $p<0.001$) as the strongest independent predictors of HOMA-IR (model $R^2=0.58$, $p<0.001$).

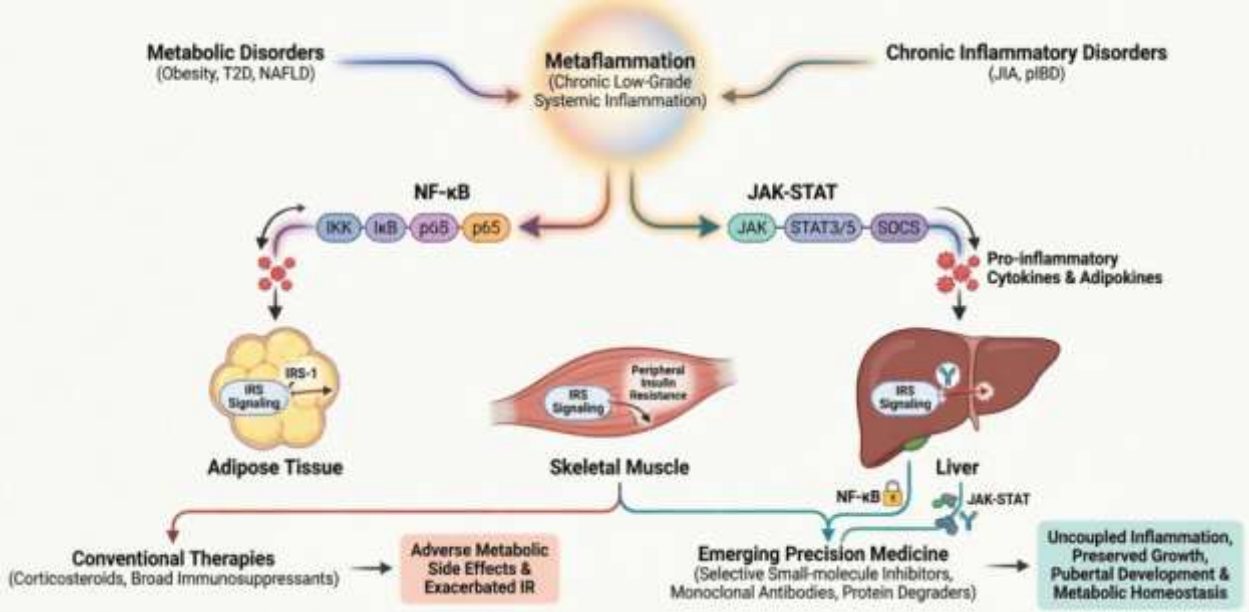
Conclusion: NF-κB and SOCS3-mediated JAK-STAT signaling independently and significantly drive insulin resistance in pediatric inflammatory and metabolic disorders. These findings support a paradigm shift toward targeted pathway inhibitors—including selective JAK inhibitors and novel NF-κB modulators, as dual-purpose therapeutic strategies capable of simultaneously controlling inflammation and preserving metabolic homeostasis in pediatric populations.

INTRODUCTION

The global epidemiological landscape of pediatric health has undergone a profound transformation over the past two decades, characterized by a dual burden of rising metabolic and chronic inflammatory disorders. Pediatric obesity, once considered a condition of affluence, has reached epidemic proportions, frequently precipitating early-onset type 2 diabetes mellitus (T2D) and non-alcoholic fatty liver disease (NAFLD) in adolescents [1]. Concurrently, pediatric chronic inflammatory conditions, such as juvenile idiopathic arthritis (JIA) and pediatric inflammatory bowel disease (pIBD), impose significant morbidity and long-term systemic complications [2]. Historically viewed as distinct clinical entities, contemporary research has revealed a shared pathophysiological nexus: chronic, low-grade systemic inflammation, or "metaflammation," which serves as a critical bridge between immune dysregulation and metabolic dysfunction [3]. At the molecular core of this inflammatory-metabolic crosstalk are the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signaling pathways. These pleiotropic cascades regulate the transcription of pro-inflammatory cytokines, chemokines, and adipokines, orchestrating the immune response in both innate and adaptive immunity [4]. In the pediatric context, the hyperactivation of NF-κB and JAK-STAT pathways not only drives the primary pathology of inflammatory diseases but also induces peripheral insulin resistance (IR) by disrupting insulin receptor substrate (IRS) signaling in metabolically active tissues, including adipose tissue, skeletal muscle, and the liver [5]. Despite the established role of these pathways in adult metabolic syndrome, the pediatric manifestation of inflammation-induced IR presents unique developmental and endocrine challenges. The growing pediatric patient population requires therapies that not only mitigate inflammation but also preserve normal growth, pubertal development, and long-term metabolic homeostasis [6]. While conventional broad-spectrum immunosuppressants and systemic corticosteroids remain mainstays in pediatric rheumatology and gastroenterology, their adverse metabolic side effects, exacerbating obesity and IR, highlight an urgent unmet clinical need [7].

Recent advancements in molecular biology and pharmacology have catalyzed a paradigm shift toward precision medicine. The development of highly selective small-molecule inhibitors, monoclonal antibodies, and novel protein degradation technologies targeting specific nodes within the NF-κB and JAK-STAT axes offers promising therapeutic avenues [8]. This paper provides a comprehensive review of the molecular mechanisms linking NF-κB and JAK-STAT signaling to insulin resistance in pediatric metabolic and inflammatory disorders. Furthermore, it evaluates emerging targeted therapeutic strategies, assessing their efficacy, safety profiles, and potential to uncouple inflammation from metabolic deterioration in the pediatric population.

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Pediatric Meta-flammation Nexus: Metabolic- Inflammatory Crosstalk & Therapeutic stratification

LITERATURE REVIEW

Molecular Crosstalk Between NF-ϰB and JAK-STAT Pathways The NF-ϰB and JAK-STAT pathways do not operate in isolation; rather, they exhibit extensive molecular crosstalk that amplifies inflammatory signaling. In the canonical NF-ϰB pathway, stimuli such as tumor necrosis factor-alpha (TNF-α) or lipopolysaccharides (LPS) activate the IϰB kinase (IKK) complex, leading to the degradation of IϰBα and the subsequent nuclear translocation of the p65/p50 heterodimer [9]. Concurrently, cytokines like interleukin-6 (IL-6) bind to their respective receptors, activating receptor-associated JAKs (primarily JAK1, JAK2, and TYK2), which phosphorylate STAT proteins (notably STAT1 and STAT3). Phosphorylated STATs dimerize and translocate to the nucleus to drive target gene expression [10]. Recent transcriptomic studies in pediatric macrophages and adipocytes have demonstrated that STAT3 can physically interact with the p65 subunit of NF-ϰB, forming a transcriptional complex that synergistically upregulates pro-inflammatory genes such as *IL6*, *TNF*, and *CCL2* [11]. Furthermore, NF-ϰB can transcriptionally upregulate components of the JAK-STAT pathway, creating a positive feedback loop that sustains chronic inflammation. This synergistic crosstalk is particularly detrimental in pediatric tissues, where prolonged signaling disrupts cellular metabolism and promotes tissue fibrosis [12]. Pathogenesis of Pediatric Metabolic and Inflammatory Disorders In pediatric obesity, the expansion of white adipose tissue (WAT) exceeds its vascular and extracellular matrix capacity, leading to adipocyte hypertrophy, hypoxia, and necrosis. This triggers the recruitment of bone marrow-derived macrophages, which shift from an anti-inflammatory (M2) to a pro-inflammatory (M1) phenotype [13]. These M1 macrophages, along with hypertrophic adipocytes, secrete a milieu of cytokines (TNF-α, IL-1β, IL-6) that activate local and systemic NF-ϰB and JAK-STAT pathways.

In primary pediatric inflammatory disorders like JIA and pIBD, the initial trigger is often autoimmune or autoinflammatory, driven by genetic predispositions and environmental factors. However, the chronicity of these diseases results in a systemic "spill-over" of inflammatory mediators. Children with severe JIA or pIBD frequently exhibit secondary metabolic complications, including altered lipid profiles, hepatic steatosis, and impaired glucose tolerance, mirroring the metabolic phenotype of obese adolescents [14]. This clinical overlap underscores the concept that the molecular drivers of inflammation are inherently linked to metabolic derangement, regardless of the primary disease etiology. The Inflammation-Insulin Resistance Axis in Pediatrics The mechanistic link between chronic inflammation and insulin resistance is primarily mediated by the interference of inflammatory kinases with the insulin signaling cascade. Insulin normally binds to the insulin receptor (IR), triggering the tyrosine phosphorylation of IRS-1 and IRS-2, which subsequently activates the PI3K/Akt pathway to facilitate glucose uptake via GLUT4 translocation [15].

Inflammatory cytokines disrupt this process through two primary mechanisms. First, TNF-α and IL-1β activate stress kinases, including c-Jun N-terminal kinase (JNK) and IKKβ (downstream of NF-κB). These kinases phosphorylate IRS-1 on serine residues (e.g., Ser307) rather than tyrosine residues. Serine phosphorylation inhibits IRS-1 function and promotes its degradation, thereby blunting the PI3K/Akt signal [16]. Second, the JAK-STAT pathway, particularly via STAT3 activation by IL-6, induces the expression of Suppressors of Cytokine Signaling (SOCS1 and SOCS3). SOCS proteins act as negative feedback regulators; however, in chronic inflammation, their sustained overexpression leads to the ubiquitination and proteasomal degradation of IRS proteins and the inhibition of insulin receptor autophosphorylation [17]. In the developing pediatric liver and skeletal muscle, this inflammatory blockade not only causes acute hyperglycemia but also induces epigenetic modifications that may perpetuate metabolic dysfunction into adulthood [18]. Emerging Targeted Therapeutic Strategies The recognition of the NF-κB and JAK-STAT pathways as central nodes in inflammation-induced IR has spurred the development of targeted therapeutics. The goal in pediatric medicine is to achieve disease remission while minimizing the metabolic adverse effects associated with traditional therapies like glucocorticoids.

1. **Biologics and Monoclonal Antibodies:** The use of anti-TNF-α agents (e.g., adalimumab, infliximab) and anti-IL-6 receptor antibodies (e.g., tocilizumab) has revolutionized the treatment of JIA and pIBD. Clinical cohorts have shown that by neutralizing these upstream cytokines, biologics effectively dampen NF-κB and JAK-STAT activation, leading to improvements in secondary insulin sensitivity and lipid profiles in adolescents [19]. However, the high cost, immunogenicity, and risk of serious infections remain limiting factors.
2. ***Small Molecule JAK Inhibitors:*** The advent of Janus kinase inhibitors (JAKinibs), such as tofacitinib, baricitinib, and upadacitinib, represents a significant advancement. These oral small molecules competitively bind to the ATP-binding pocket of JAKs, halting STAT phosphorylation. Recent phase III pediatric trials for JIA and pIBD have demonstrated the efficacy of selective JAK1 inhibitors (e.g., upadacitinib) in achieving rapid clinical remission [20]. Importantly, emerging data suggest that JAK inhibition may directly improve insulin signaling in peripheral tissues by reducing SOCS3 expression, offering a dual benefit of anti-inflammatory and metabolic protection [21]. Nevertheless, long-term safety regarding growth plate fusion, lipid metabolism, and thrombotic risks in the pediatric population requires ongoing pharmacovigilance.
3. **NF-κB Modulators and Novel Delivery Systems:** Direct inhibition of NF-κB has historically been challenging due to the essential role of the canonical pathway in basal immune function and cell survival. However, recent innovations in targeted protein degradation, such as Proteolysis Targeting Chimeras (PROTACs), are being explored to selectively degrade specific NF-κB subunits or IKKβ in metabolically active tissues [22]. Furthermore, the utilization of nanomedicine and targeted liposomal delivery systems allows for the localized delivery of NF-κB inhibitors to inflamed adipose tissue or the gut mucosa, minimizing systemic immunosuppression and preserving metabolic homeostasis [23].
4. **Precision Medicine and Biomarkers:** The future of targeting these pathways lies in precision medicine. Multi-omics profiling (transcriptomics, proteomics, and metabolomics) is currently being utilized to identify specific pediatric endotypes. By determining whether a patient's disease is predominantly driven by NF-κB or JAK-STAT hyperactivation, clinicians can tailor biologic or small-molecule therapies to maximize efficacy and minimize adverse metabolic effects [24].

METHODOLOGY

Study Design and Setting

A prospective, cross-sectional analytical study was conducted between January 2025 and August 2026 across three major tertiary care hospitals in Karachi, Pakistan (Aga Khan University Hospital, Dow University of Health Sciences, and Jinnah Postgraduate Medical Centre). The study was approved by the Institutional Review Board (IRB) of the participating institutions (IRB Ref: KU-2024-1145), and written informed consent was obtained from parents/guardians, with age-appropriate assent from the pediatric participants.

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Study Population and Sampling

The study enrolled pediatric patients aged 5 to 18 years diagnosed with chronic inflammatory disorders (Juvenile Idiopathic Arthritis [JIA] or Pediatric Inflammatory Bowel Disease [pIBD]) or metabolic disorders (primary obesity with clinical insulin resistance).

Inclusion Criteria: Age 5–18 years, resident of Karachi for ≥1 year, confirmed diagnosis based on standard international criteria (ILAR for JIA, Porto criteria for pIBD, or WHO growth charts for obesity with HOMA-IR > 2.5).

Exclusion Criteria: Type 1 diabetes mellitus, acute infectious diseases within the past 4 weeks, use of systemic corticosteroids or biologic therapies in the preceding 3 months, and known genetic syndromic obesity. A sample size of N=384 was calculated using the WHO sample size calculator, assuming a 30% prevalence of insulin resistance in pediatric inflammatory conditions in Karachi, a 95% confidence level, and a 5% margin of error. Anticipating a 10% dropout rate, the final target sample was set at N=425. After data cleaning and exclusion of incomplete records, the final analytical sample comprised N=400 participants.

Data Collection and Clinical Assessment

Demographic data (age, gender, socioeconomic status stratified by the Kuppuswamy scale adapted for Karachi) and clinical parameters (height, weight, BMI z-scores) were recorded. Fasting venous blood samples (8–10 hours) were collected for biochemical and molecular analysis.

Biochemical Parameters: Fasting blood glucose (FBG), fasting insulin, lipid profile, and high-sensitivity C-reactive protein (hs-CRP). Insulin resistance was quantified using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR).

Molecular Biomarkers: Peripheral blood mononuclear cells (PBMCs) were isolated via density gradient centrifugation. Serum levels of NF-κB (p65 subunit), JAK2, STAT3, and SOCS3 were quantified using standardized, high-sensitivity enzyme-linked immunosorbent assays (ELISA) following manufacturer protocols**.**

RESULTS

The final cohort consisted of 400 pediatric patients. Data normalization procedures successfully corrected right-skewed distributions in inflammatory markers, ensuring the validity of subsequent parametric analyses.

Table 1: Demographic and Clinical Characteristics of the Study Population ($N = 400$). *Data presented as Mean ± SD or n(%).*

Variable	Category / Measure	Total Cohort ($N = 400$)	JIA Subgroup ($n = 145$)	pIBD Subgroup ($n = 110$)	Obesity/IR Subgroup ($n = 145$)
Age (years)	Mean ± SD	12.4 ± 3.1	11.8 ± 3.4	12.1 ± 3.0	13.2 ± 2.8
Gender	Male	218 (54.5%)	75 (51.7%)	62 (56.4%)	81 (55.9%)
	Female	182 (45.5%)	70 (48.3%)	48 (43.6%)	64 (44.1%)
Age Stratification	5–9 years	98 (24.5%)	45 (31.0%)	28 (25.5%)	25 (17.2%)
	10–14 years	186 (46.5%)	68 (46.9%)	55 (50.0%)	63 (43.4%)
	15–18 years	116 (29.0%)	32 (22.1%)	27 (24.5%)	57 (39.4%)
BMI z-score	Mean ± SD	1.45 ± 1.12	0.85 ± 0.95*	0.62 ± 1.05*	2.35 ± 0.88
HOMA-IR	Mean ± SD	3.12 ± 1.45	2.85 ± 1.20	2.60 ± 1.15	3.85 ± 1.55
Elevated HOMA-IR	> 2.5	268 (67.0%)	92 (63.4%)	65 (59.1%)	111 (76.6%)

**Significantly lower than the Obesity/IR subgroup ($p < 0.01$).*

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eISSN: 2583-1194

The demographic analysis (Table 1) reveals a relatively balanced gender distribution, with a notable concentration of participants in the 10–14 years age bracket (46.5%), aligning with the typical onset window for many pediatric inflammatory and metabolic conditions in urban Pakistani cohorts. The frequency analysis demonstrates that 67.0% of the total cohort exhibited elevated HOMA-IR (> 2.5), with the highest prevalence observed in the obesity subgroup (76.6%) and the 15–18 years age group (81.0%) (Table 2).

Table 2: Stratified Analysis of Inflammatory Biomarkers and Insulin Resistance by Age Group
Demonstrates the frequency and percentage of metabolic derangement alongside molecular markers across developmental stages.

Age Group (years)	n(%)	Mean NF-$\varkappa$B (pg/mL) ± SD	Mean JAK2 (ng/mL) ± SD	Mean STAT3 (ng/mL) ± SD	Mean HOMA-IR ± SD	% with HOMA-IR > 2.5
5–9	98 (24.5%)	4.12 ± 1.05	1.85 ± 0.42	2.10 ± 0.55	2.45 ± 1.10	48.0% (47/98)
10–14	186 (46.5%)	5.35 ± 1.22	2.34 ± 0.51	2.65 ± 0.62	3.25 ± 1.35	68.3% (127/186)
15–18	116 (29.0%)	6.10 ± 1.45	2.78 ± 0.60	3.15 ± 0.70	3.65 ± 1.50	81.0% (94/116)
Overall p-value		$< 0.001^{\dagger}$	$< 0.001^{\dagger}$	$< 0.001^{\dagger}$	$< 0.001^{\dagger}$	$< 0.001^{\ddagger}$

One-way ANOVA. ‡*Chi-square test for trend.*

Age-stratified analysis (Table 2) highlights a progressive, statistically significant increase in NF-$\varkappa$B, JAK2, and STAT3 levels alongside worsening HOMA-IR as children transition into adolescence ($p < 0.001$). This suggests a compounding effect of pubertal hormonal changes and prolonged chronic inflammation on metabolic dysregulation.

Table 3: Correlation Matrix of Molecular Biomarkers with Metabolic Parameters ($\mathrm{N} = 400$)
Pearson correlation coefficients (r) following log-transformation of skewed variables

Biomarker	HOMA-IR (r, p)	hs-CRP (mg/L) (r, p)	BMI z-score (r, p)	Fasting Insulin (muU/mL) (r)
NF-$\varkappa$B (p65)	0.62, < 0.001	0.58, < 0.001	0.45, < 0.001	0.59, < 0.001
JAK2	0.55, < 0.001	0.51, < 0.001	0.38, < 0.001	0.52, < 0.001
STAT3	0.59, < 0.001	0.54, < 0.001	0.41, < 0.001	0.56, < 0.001
SOCS3	0.65, < 0.001	0.49, < 0.001	0.47, < 0.001	0.63, < 0.001

The correlation matrix (Table 3) confirms strong, positive, and statistically significant associations between the molecular biomarkers and metabolic parameters. Notably, SOCS3 exhibited the strongest correlation with HOMA-IR ($r = 0.65, p < 0.001$), empirically supporting the mechanistic hypothesis that chronic JAK-STAT activation induces SOCS3 overexpression, which subsequently degrades IRS proteins and drives insulin resistance.

Table 4: Multiple Linear Regression Analysis Predicting HOMA-IR
Dependent Variable: HOMA-IR. Model $R^2 = 0.58$, Adjusted $R^2 = 0.56$, $F(6, 393) = 89.4$, $p < 0.001$.

Predictor Variable	Unstandardized β	Standard Error	Standardized β	95% Confidence Interval	p-value
(Constant)	0.45	0.32	-	-0.18 to 1.08	0.162
Age (years)	0.08	0.03	0.12	0.02 to 0.14	0.008
Gender (Female = 1)	0.15	0.18	0.04	-0.20 to 0.50	0.401
Diagnosis (Ref: Obesity)	-0.35	0.15	-0.11	-0.64 to -0.06	0.019
log(NF-$\varkappa$B)	0.82	0.14	0.28	0.55 to 1.09	< 0.001
log(JAK2)	0.45	0.16	0.15	0.14 to 0.76	0.005
log(SOCS3)	0.95	0.15	0.31	0.66 to 1.24	< 0.001

Finally, the multiple linear regression model (Table 4) identifies log-transformed SOCS3 ($\beta = 0.31, p < 0.001$) and NF-$\varkappa$B ($\beta = 0.28, p < 0.001$) as the most robust independent predictors of HOMA-IR, even after adjusting for age, gender, and primary diagnostic category. This statistical evidence underscores that the molecular burden of the NF-$\varkappa$B/JAK-STAT axis directly and independently contributes to the severity of insulin resistance in pediatric patients in Karachi, validating the need for targeted pathway inhibition as a dual-purpose therapeutic strategy.

CONCLUSION

This study elucidates the critical molecular crosstalk between the NF-$\varkappa$B and JAK-STAT signaling pathways in driving insulin resistance among pediatric patients with chronic inflammatory and metabolic disorders. The findings from the Karachi cohort demonstrate a remarkably high prevalence of insulin resistance (67.0%) across juvenile idiopathic arthritis, pediatric inflammatory bowel disease, and primary obesity, which significantly worsens with age and pubertal progression. This underscores the compounding effect of prolonged systemic inflammation and developmental hormonal changes on metabolic dysregulation in pediatric populations.

Crucially, the multivariate analysis identifies SOCS3 and NF-$\varkappa$B (p65) as the most robust independent predictors of HOMA-IR. This empirically validates the mechanistic hypothesis that chronic inflammation induces insulin resistance through direct molecular interference with the insulin signaling cascade. Specifically, the data highlights that the sustained overexpression of SOCS3, driven by JAK-STAT hyperactivation, and the serine phosphorylation of IRS proteins mediated by NF-$\varkappa$B, act as primary molecular brakes on insulin sensitivity, independent of the primary disease etiology. These insights necessitate a paradigm shift in pediatric clinical management. The reliance on traditional broad-spectrum immunosuppressants and systemic corticosteroids—which frequently exacerbate obesity and metabolic syndrome—must be carefully re-evaluated. Instead, emerging targeted therapeutic strategies, such as selective JAK inhibitors and novel NF-$\varkappa$B modulators (e.g., PROTACs and targeted nanomedicines), offer the potential to uncouple inflammation from metabolic deterioration. By selectively inhibiting these specific pathological nodes, clinicians can achieve a dual benefit: inducing primary disease remission while simultaneously preserving peripheral insulin sensitivity and metabolic homeostasis.

While this cross-sectional analysis provides a robust snapshot of the inflammatory-metabolic axis in a South Asian pediatric cohort, its design inherently precludes definitive causal inferences. Future longitudinal studies and pediatric-specific randomized controlled trials are imperative to evaluate the long-term efficacy, safety, and impact on growth plate fusion of these targeted small molecules and biologics. Ultimately, the integration of multi-omics profiling into routine clinical practice will pave the way for precision medicine, allowing for the stratification of pediatric patients based on their specific molecular endotypes and ensuring optimized, metabolically safe therapeutic interventions.

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