REVIEW ARTICLE

Metabolic-Immune Crosstalk in Pediatric Rheumatology: From Pathogenesis to Precision Therapy

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ABSTRACT

The immune system and metabolic pathways are strongly interconnected, influencing each other in both physiological and pathological contexts. Nutrient signaling and cellular energy levels significantly impact immune system function, from activation to differentiation and survival. In children, where both the immune and metabolic systems are still developing, disturbances in this balance can markedly influence disease manifestation and treatment response. Recent advances in immunometabolism have revealed that metabolic dysfunction is not merely a consequence of inflammation but can also serve as a primary driver of immune dysregulation. Accordingly, this review explores how metabolic disturbances may mimic or modify rheumatic diseases, and, conversely, how immune-mediated disorders can disrupt metabolic homeostasis. Understanding this bidirectional relationship provides novel insights into pathogenesis and opens avenues for metabolism-based diagnostic and therapeutic strategies in pediatric rheumatology.

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Introduction

Traditionally, pediatric rheumatology has focused on immune dysregulation as the leading cause of inflammation. Emerging evidence shows that metabolism — the way cells process nutrients, produce energy, and maintain balance— is also vital in the immune system function (1). The idea of immune metabolism has changed the understanding of inflammation (2). Through metabolic pathways, immune cells can be activated to perform their functions (3). For instance, immune cells like effector cells and M1 macrophages rely on glycolysis for energy. In contrast, regulatory T cells and M2 macrophages use oxidative metabolism and fatty acid oxidation to support the long-term balance of immune function.

In children, immune system function and growth work simultaneously. Any dysregulation in metabolic balance can interfere with metabolic homeostasis, leading to chronic inflammation, and potentially causing autoinflammatory and autoimmune disorders. This connection between metabolic and immune systems can explain disorders such as juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), and autoinflammatory syndromes. Understanding this connection can guide physicians in finding better ways to diagnose and treat autoimmune and autoinflammatory diseases in children (4).

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Immunometabolism: The interface between energy and inflammation

The immune system needs energy to perform its function. With adequate energy and nutrients, immune cells can be activated and work properly. Without sufficient energy or impaired metabolism, the immune system cannot respond in a balanced way (5). Different immune cells use other energy sources. For example, during the infectious process, effector T cells and M1 macrophages rapidly shift to glycolysis, a fast but less efficient pathway allowing them to respond quickly (6). On the other hand, regulatory T cells and M2 macrophages depend on oxidative phosphorylation and fatty acid oxidation, slower but more efficient ways to produce energy to maintain long-term balance (7). In children, the metabolism and immune system are still developing together (8). Any change in this balance, such as infection, poor nutrition, or genetic metabolic disorders, can trigger an inflammatory response or autoimmune manifestations (9). This explains why some metabolic diseases in children can initially appear similar to rheumatologic diseases (10).

Metabolic diseases that mimic rheumatic disorders

In children, several metabolic disorders can closely mimic autoimmune or rheumatologic diseases. These conditions may present with musculoskeletal or systemic manifestations that resemble pediatric rheumatic disorders, often resulting in delayed diagnosis. For instance, Farber disease may manifest with painful subcutaneous nodules and joint swelling resembling JIA (11). Gaucher disease can present with bone pain, osteopenia, and radiologic findings suggestive of inflammatory arthropathy. However, splenomegaly and/or cytopenia usually help differentiate it from JIA (12). Fabry disease is another example, in which paresthesia and arthralgia may simulate vasculitic processes (13). Glycogen storage diseases (GSD) with myopathies, such as type III and Pompe disease (type II), type IV, and specifically type V McArdle, along with types VII and IX, can manifest with muscle weakness. Still, progressive muscle weakness with concomitant heart or liver involvement could suggest GSD (14).

In children with Mucopolysaccharidosis (type I, II, IV, VI, IX), joint contracture and stiffness may mimic JIA or scleroderma, but these patients do not have true synovitis and may have kyphoscoliosis and skeletal dysplasia (15). Mitochondrial cytopathies and fatty acid oxidation disorders (with myalgia and elevated CPK) can cause weakness, elevated CPK, and myalgia, looking like inflammatory myopathies (16). Furthermore, Pyruvate dehydrogenase deficiency is another metabolic disorder resembling inflammatory myopathy, characterized by lactic acidosis, muscle weakness, and fatigue(17). Lesh-Nyhan syndrome and PRPS1 superactivity can both present with gout-like arthritis due to uric acid overproduction(18). Systemic infantile Hyalinosis can cause painful contractures and stiff skin like scleroderma. Fibrodysplasia ossificans progressive can manifest with painful soft-tissue swelling, joint stiffness, and progressive ankylosis, resembling JIA (19). In Prolidase deficiency, ulcers, skin rashes, and arthralgia can cause a lupus-like disease (20). Hereditary connective tissue disorders like Ehlers-Danlos syndrome and osteogenesis imperfecta (OI) may appear with joint hypermobility, recurrent subluxation, and joint pain that mimics JIA (21). Peroxisomal (Rhizomelic achondroplasia puncta: With severe short stature, joint contracture, and femoral dysgenesis) and lipid metabolism defects, such as Zellweger syndrome, Adrenoleukodystrophy, and Tangier, can present with muscle weakness or contractures that resemble inflammatory myopathies (22). Storage disorders like Wilson disease and hemochromatosis can lead to chronic arthropathy similar to JIA, while Homocystinuria and Alkaptonuria, with connective tissue and pigmentary changes, lead to arthropathy resembling JIA (23, 24). Gout in children is quite rare. However, because of crystal deposits in the joints, it can resemble JIA. Inborn errors such as Mevalonate kinase deficiency and Multiple sulfatase deficiency can present with recurrent fever, rash, and arthralgia, similar to systemic onset JIA (25). Finally, metabolic dysplastic bone disorders may lead to skeletal deformities, such as chronic inflammatory arthropathies (26) (Table 1).

Recognizing these conditions is crucial for clinicians to achieve timely, accurate diagnoses and to design more precise, mechanism-based treatment approaches.

Rheumatologic diseases mimicking metabolic disorders

Just like metabolic disorders that can look like Rheumatic diseases, many Rheumatologic disorders may present with clinical or laboratory findings resembling metabolic disorders. Patients may present with growth failure, hypertriglyceridemia, elevated liver enzymes, elevated muscle enzymes, or steatosis, leading to initial suspicion of metabolic disorder. Some autoinflammatory disorders can mimic metabolic defects. For instance, NLRP-3-associated periodic fever syndrome, characterized by excessive IL-1 production, may present with recurrent fevers, growth retardation, osteochondropathy, and central nervous system involvement, resembling metabolic diseases (27). Similarly, NLRC4-MAS syndrome, featuring

overactivation of IL-18 and the inflammasome pathway, can present with conditions akin to hemophagocytic lymphohistiocytosis (HLH), which can also be associated with metabolic defects (28). Partially mevalonate kinase deficiency (hyper-IgD syndrome) may lead to symptoms such as fever, lymphadenopathy, diarrhea, hyperuricemia, steatosis, and hypertriglyceridemia, potentially confusing it with metabolic disorders (29). These disorders stem from defects in the IL-1 and mevalonate pathways. Additionally, deficiency of adenosine deaminase 2, a purine metabolism disorder, can manifest with stroke, pancytopenia, elevated liver enzymes, and vasculitis (30).

Table 1. Metabolic disorder with rheumatologic manifestation

Disease	Shared feature	Mechanism
Farber disease	Painful subcutaneous nodules, joint swelling	Accumulation of ceramide
Gaucher disease	Bone pain, osteopenia, and inflammatory arthritis	Accumulation of glucocerebroside
Fabry disease	Paresthesia, arthralgia	Glycosphingolipid deposition
Glycogen storage disease	Muscle weakness	Accumulation of glycogen
Mucopolysaccharidosis	Joint contracture, stiffness	Accumulation of glycosaminoglycan
Mitochondrial cytopathies	Muscle weakness	Impaired oxidative phosphorylation
Fatty acid oxidation defect	Muscle weakness	Lipid accumulation myopathy
Pyruvate dehydrogenase deficiency	Muscle weakness	Impaired aerobic metabolism
Lesh-Nyhan syndrome	Gout-like arthritis	Purine overproduction
PRPS1 super activity	Gout-like arthritis	Overproduction of purines
Fibrodysplasia ossificans progressive	Soft tissue swelling, joint stiffness, and ankylosis	Ectopic bone formation in soft tissue
Prolidase deficiency	Lupus-like features	Collagen degradation defect
Hereditary connective tissue disorders	Hypermobility, joint pain	Collagen, elastin defect
Peroxisomal metabolic defects	Muscle weakness, joint contracture	Accumulation of very long-chain fatty
Lipid metabolic defects	Muscle weakness, joint contracture	Lipid deposition
Storage disorders	Arthritis	Intracellular substrate accumulation
Homocystinuria	Arthropathy	Collagen cross-link defect
Alkaptonuria	Arthropathy	Homogentisic acid deposition
Gout	Arthropathy	Monosodium orate crystal deposition
Mevalonate Kinase deficiency	Fever, rash, arthritis (like SJIA)	Impaired isoprenoid biosynthesis
Multiple sulfatase deficiency	Fever, rash, arthritis (like SJIA)	Accumulation of sulfatides
Metabolic dysplastic bone disorder	Arthropathy	Abnormal bone matrix metabolism

Among autoimmune disorders, several conditions exhibit characteristics similar to metabolic defects. Juvenile dermatomyositis (JDM), characterized by immune-mediated destruction of blood vessels and muscle tissues, can lead to elevated levels of creatine phosphokinase and other muscle enzymes, which may mimic mitochondrial dysfunction (31). Additionally, JDM is associated with hepatic steatosis and dyslipidemia, further underscoring its metabolic implications.

In SLE, the presence of systemic inflammation can lead to a variety of complications, including secondary mitochondrial dysfunction, hepatic steatosis, Reye syndrome, cytopenia, thyroid dysfunction, and hyperammonemia. These conditions can arise as a consequence of the underlying autoimmune process, which may disrupt normal metabolic pathways and cellular function. Understanding these associations is crucial for the effective management of SLE and its systemic manifestations.

Autoimmune lipodystrophy, particularly in the context of Aicardi-Goutières syndrome overlap, is characterized by an immune-mediated reaction against adipocytes (32). This pathological response can lead to significant metabolic disturbances, including severe dyslipidemia, insulin resistance, and the clinical manifestations of lipodystrophy. The interplay between autoimmune processes and metabolic derangements highlights the complex nature of this condition and underscores the necessity for further research into its underlying mechanisms and therapeutic approaches.

Certain rheumatologic disorders affecting the bone can sometimes mimic metabolic disorders. For instance, chronic recurrent multifocal osteomyelitis may present with skeletal defects similar to those seen in osteoporosis and osteitis, resembling metabolic diseases (33). Majid syndrome can also involve the bone and is associated with sideroblastic anemia and skin rash (34). Additionally, Camurati-Engelmann disease (related to TGFB1) can affect skeletal structures in a manner that resembles metabolic defects (35).

Interferonopathies, such as SAVI, TREX1 mutations, and Aicardi-Goutières syndrome, may manifest with developmental delay, myopathy, skin vasculitic rashes, and osteopenia (36). All these disorders remind us of the importance of recognizing the overlapping

signs and symptoms of both metabolic and rheumatologic diseases (Table 2).

Clinical clues for differentiating metabolic and rheumatologic disorders

Due to similar symptoms between metabolic and rheumatic diseases, distinguishing between them is challenging. However, several clinical and laboratory clues can help physicians recognize when inflammation might be secondary to a metabolic problem rather than a primary immune disease. Conditions may present with musculoskeletal pain, weakness, and systemic inflammation. Metabolic disorders are typically noticed in children born to consanguineous parents, and a positive family history of metabolic disorders is usually present among relatives (37). A distinct unpleasant odor often accompanies these disorders and may increase the risk of sudden infant death (38). Additionally, hypoglycemia may also occur concurrently. These disorders frequently affect multiple organs, leading to symptoms such as hepatomegaly, developmental delay, seizures, hypotonia, or a distinctive body odor. While these manifestations can occur in the context of an autoimmune disease, several symptoms, specifically a strong body odor, are uncommon. For example, although systemic-onset is present in other subtypes, we do not typically expect to see hepatomegaly. Therefore, the discovery of hepatomegaly in this context may suggest an underlying metabolic disorder.

In laboratory investigations, persistently elevated lactate, metabolic acidosis, abnormal acylcarnitine profile, or increased creatine kinase suggest an underlying enzymatic defect rather than autoimmunity.

In contrast, rheumatologic diseases such as SLE, JIA, and JDM often present with symptoms including joint involvement, morning stiffness, rashes, Raynaud's phenomenon, or serologically detectable autoantibodies such as ANA, anti-dsDNA, or rheumatoid factor (RF) (39). These conditions typically respond well to immunosuppressive medications. Consequently, warning signs such as failure to thrive, early onset, and unexplained liver or neurological involvement should raise suspicion for a metabolic disorder. A multidisciplinary diagnostic approach combining the expertise of rheumatologists, geneticists, and metabolic specialists can provide the most effective strategy for managing these patients.

Table 2. Rheumatologic disorders mimicking Metabolic defects

Disease	Shared feature	Mechanism
NLPR3 associated periodic fever syndrome	Growth retardation, osteochondropathy	Overactivation of the inflammasome (IL-1)
NLRC4-MAS syndrome	HLH-like attack	Inflammasome overproduction (IL-18)
Partially mevalonate kinase deficiency	Hyperuricemia, diarrhea, hypertriglyceridemia	Defective isoprenoid synthetase
Deficiency of adenosine deaminase 2	Stroke, cytopenia, and elevated liver enzymes	Adenosine accumulation
Juvenile dermatomyositis	Muscle weakness	Immune-mediated microangiopathy
Systemic lupus erythematosus	Cytopenia, Reye syndrome, hyperammonemia	Chronic inflammation, autoantibody
Aicardi-Goutières syndrome	Dyslipidemia, insulin resistance, lipodystrophy	Accumulation of nucleic acid
Chronic recurrent multifocal osteomyelitis	Skeletal defect	Dysregulated innate immunity
Majid syndrome	Skeletal defect	LPIN2 mutation
Camurati-Engelmann disease	Skeletal defect	TGFB1 mutation
Interferonopathies	Developmental delay, myopathy, osteopenia	Constitutive type 1 interferonopathy

SJIA: systemic juvenile idiopathic arthritis

How metabolism controls immune activity

Metabolism and the immune system are intricately interconnected (40). The immune system relies on energy to function effectively and adjusts its behavior according to the availability of energy and nutrients. When energy supply is sufficient, immune cells can grow, divide, and respond effectively to infections. Conversely, during periods of energy scarcity, the body enters a protective mode, conserving resources and reducing inflammation to prevent further damage.

Three key pathways regulate cellular internal environments: mTOR, AMPK, and HIF-1α. mTOR (mechanistic target of rapamycin) acts as a growth switch. With adequate nutrients, it activates the immune system, stimulating cell growth and the production of inflammatory cytokines. In contrast, AMPK (AMP-activated protein kinase) operates when energy levels are low, helping the cell conserve energy and suppress unnecessary inflammation (41). Meanwhile, HIF-1α (hypoxia-inducible factor 1-alpha) becomes active when nutrients are scarce, assisting the immune system in adapting to stress by switching to glycolysis (42).

Together, these proteins determine whether the immune system responds aggressively or calmly. In children, where growth and energy demands are high,

disturbances in these pathways, such as mitochondrial dysfunction, enzyme deficiencies, or nutrient imbalances can disrupt immune homeostasis, manifesting as inflammatory or rheumatologic-like symptoms. Understanding this close interaction is essential for identifying metabolic contributions to immune dysregulation. Metabolism and the immune system are closely connected. The immune system relies on energy to function effectively and adjusts its behavior according to the availability of energy and nutrients. When energy resources are sufficient, immune cells can proliferate, differentiate, and mount efficient responses against infections. However, during periods of energy scarcity, the body enters a protective mode, conserving resources and reducing inflammation to prevent further damage.

Table 3: Rheumatologic disorders mimicking Metabolic defects

Disease	Shared Feature	Mechanism
NLPR3 Associated Periodic Fever Syndrome	Growth retardation, osteochondropathy	Overactivation of the inflammasome (IL-1)
NLRC4-MAS syndrome	HLH-like attack	Inflammasome overproduction (IL-18)
Partially mevalonate kinase deficiency	Hyperuricemia, diarrhea, hypertriglyceridemia	Defective isoprenoid synthetase
deficiency of adenosine deaminase 2	Stroke, cytopenia, and elevated liver enzymes	Adenosine accumulation
Juvenile dermatomyositis	Muscle weakness	Immune-mediated microangiopathy
systemic lupus erythematosus	Cytopenia, Reye syndrome, hyperammonemia	Chronic inflammation, autoantibody
Aicardi-Goutières syndrome	Dyslipidemia, insulin resistance, lipodystrophy	Accumulation of nucleic acid
chronic recurrent multifocal osteomyelitis (CRMO)	Skeletal defect	Dysregulated innate immunity
Majid syndrome	Skeletal defect	LPIN2 mutation
Camurati-Engelmann disease	Skeletal defect	TGFB1 mutation
Interferonopathies	Developmental delay, myopathy, osteopenia	Constitutive type 1 interferonopathy

HLH: hemophagocytic lymphohistiocytosis

In Conclusion

Pediatric rheumatology is entering a new era in which metabolism is recognized as a key regulator of inflammation, rather than merely a background mechanism. Gaining a deeper understanding of metabolic defects in autoimmune and autoinflammatory syndromes could facilitate earlier diagnosis and improve treatment predictions. Future studies integrating metabolomics, genomics, and immune profiling investigate how metabolism influences immune tolerance and disease development in children. Collaboration between rheumatologists, geneticists, and metabolic specialists is essential to translate these discoveries into tangible clinical benefits and enhance patient outcomes (43-45).

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Authors' Contribution

Niloofar Shashaani conceptualized and drafted the initial version of this Review. Vadood Javadi Parvaneh, as the corresponding Author, supervised the whole content and approved the final version. Khosro Rahmani, Mohammadreza Alaei, and Reza Shiari contributed to the literature review, scientific editing, and intellectual revision of he manuscript.

Conflict of interest

The authors declared no conflict of interest.

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