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REVIEW

# Multispecialty approach for improving outcomes in juvenile dermatomyositis

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**Abstract:** Juvenile dermatomyositis (JDM) is a pediatric rheumatic disease characterized by inflammation of the muscle and skin. Prognosis of JDM in children has improved in general owing to medical progress; however, pathogenesis and management of JDM in children and prognosis in refractory JDM remain challenging. For elucidation of JDM pathophysiology and establishment of appropriate treatment for JDM, pediatric rheumatologists need to adopt a multispecialty approach that involves experts in genetics, immunology, pathology, musculoskeletal medicine, dermatology, pulmonology, cardiology, hematology, gastroenterology, endocrinology, ophthalmology, psychology, radiology, pharmacology, physiotherapy, surgery, preventive medicine, and adult rheumatology. Such collaborations will potentially lead to improved outcomes in children with JDM.

**Keywords:** liposteroid, pathophysiology, physiotherapy, preventive medicine, psychology

## Introduction

Juvenile dermatomyositis (JDM) is a multisystem disease of uncertain origin, characterized by chronic inflammation of the striated muscle and skin.[1] Although its prognosis has improved in general owing to medical progress, some issues regarding the pathogenesis and management of JDM in children, and prognosis in children with refractory JDM, remain unresolved. To date, pediatricians have performed the majority of JDM research and treatment approaches. This review summarizes the various fields of recent medicine that could collaboratively investigate JDM through a multispecialty approach. Although each field can make individual contributions to medical progress, a collaborative effort spearheaded by pediatric rheumatologists will help improve JDM medical care in future.

## Genetics

JDM is associated with immune-related genes of the human leukocyte antigen (HLA) region.[2] The International Myositis Genetics Consortium reported the first genome-wide analysis of JDM, which confirmed the HLA region as the strongest genetic risk region for JDM.[3] Three new genetic associations with myositis were identified, namely *PLCL1, BLK*, and *CCL21*. Complement C4A deficiency appears to be an important factor of the genetic risk and pathogenesis of JDM, particularly in patients with HLA-DR3-positive background.[4] Gene expression profiling has revealed a prominent type I interferon (IFN) signature in JDM muscles that could be related to viral exposure.[5]

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## Immunology

JDM is an autoimmune disease, with regular occurrence of autoantibodies and evidence of antigen-driven clonal B- and T-cell expansion in the inflamed muscle.[2] Characteristic abnormalities in JDM include excess type I IFN production in blood and muscles, leading to immune cell activation and vasculopathy. Type I IFN, produced by dendritic cells, stimulates the production of pro-inflammatory cytokines, and enhances the expression of HLA class I and II molecules.[6] Patients with JDM having high levels of eotaxin and monocyte chemoattractant protein 1 show early signs of organ damage.[7] The association of IFN-γ-inducible protein 10, galectin 9, or tumor necrosis factor (TNF) receptor 2 with disease activity has been confirmed in JDM.[8] Different markers of muscle inflammation, suggested in patients with JDM, include CD59, vascular cell adhesion molecule, intercellular adhesion molecule, and Toll-like receptors 2, 3, 4 or 7.[9] Examination of subcutaneous calcinosis called "milk of calcium" in JDM revealed abnormally high levels of interleukin (IL)-6, TNF-α, and IL-1β.[10] Remarkably elevated serum levels of IL-18, B-cell activating factor, and a proliferation-inducing ligand in patients with JDM were observed in rapidly progressive interstitial lung disease (ILD).[11]

Autoantibodies are detected in more than 60–70% of patients with JDM.[2,12] Moreover, patients frequently test positive for antinuclear antibodies, although no diagnostic value has yet been established. The most common myositis-specific autoantibodies (MSAs) in JDM are anti-transcription intermediary factor 1-γ (TIF1-γ) and anti-nuclear matrix protein 2 antibodies, found in 20–35% and 15–25% of patients, respectively.[5,13] Anti-TIF1-γ antibody is associated with more serious cutaneous involvement. Anti-nuclear matrix protein 2 antibody is associated with calcinosis, gastrointestinal ulceration, severe disease course, and persistent disease activity. Anti-mealnoma differentiation-associated gene 5 (MDA5) antibody is associated with ILD, skin ulceration, and arthritis. Anti-Mi-2 antibody is associated with severe muscle disease, although patients with JDM having the antibody are more susceptible to drug-free remission.[14] Histological severity predicts increased risk of being treated, whereas anti-Mi-2 antibody provides a protective effect.

## Pathology

Muscle biopsy is important for the diagnosis of JDM. Up regulation of HLA class I in muscle cells is one of the earliest changes detected by light microscopy.[2] Histologic abnormalities in JDM shows B and T cell, macrophage, and dendritic cell infiltration, and regulatory T cells are significantly increased in JDM muscle tissue compared to control muscle tissue.[15] Muscle tissues show not only immune cell infiltrates but also C5b-9 deposits.[16] Impaired function of JDM vasculature includes immune complex deposition, altered expression of cell adhesion molecules that predominantly induce T helper 17 cell infiltration, and endothelial cell dysfunction.[17] The early phase of myogenesis appears to be associated with endothelial cell activation. However, an altered expression of myogenic regulatory factors in perifascicular regions with capillary depletion suggests an impairment of myogenic differentiation that may contribute to perifascicular muscle fiber atrophy in JDM.[18] An international consensus group proposed a scoring system for JDM muscle biopsies based on four domains: inflammatory, vascular, muscular, and connective tissue; the inflammatory and muscular domains are strongly correlated with disease activity.[19] The severity of histological changes in a biopsy closely correlated with MSAs.[2,20] Small-vessel vasculitis is considered to be related to severe extramuscular manifestations of the disease such as calcinosis, skin ulceration, and ILD.[16,21] Activated macrophages play an important role in calcinosis in JDM.[22]

## Musculoskeletal medicine

Ninety-five percent of patients with JDM have symmetrical and proximal muscle weakness at the time of diagnosis.-[16] Chronic muscle weakness or dysfunction, owing to long-term active muscle disease, is clinically found in 34% of patients with JDM.[23] Muscle strength should be strictly tested using validated tools, such as the childhood myositis assessment scale or manual muscle test.[9] Electromyography or nerve conduction velocity is adopted only when diagnosis is uncertain. Arthritis is another common manifestation of JDM, with a reported prevalence of 23–64%.[16] It may occur early in the disease course and is usually non-erosive. Vertebral fractures develop in up to 10% of patients treated with glucocorticoid (GC) for 12 months, whereas osteopenia or osteoporosis developed in 6–35% of patients in long-term outcome studies.[1]

## Dermatology

Cutaneous abnormalities, mainly consisting of Gottron's papules and heliotrope rash, are apparent in approximately

75% of patients with JDM.[16] Calcinosis is a recognized complication in this disease, with a reported prevalence of 10–70%.[24] It often occurs later in the disease course, on an average of 2.9 years after disease onset.[25] Skin ulceration occurs in 33% and 12% of patients, before and after their fifth birthday, respectively,[26] and are occasionally reported as severe complications.[27] Lipodystrophy occurs in 10–30% of patients, mostly after 5 years of JDM diagnosis.[5] Most patients with JDM have nailfold capillary changes at the time of diagnosis, and represent a sensitive measure of skin, muscle, and lung disease, but not of cardiac disease activity.[28] Persistent capillary abnormalities and Gottron's papules at 6 months after diagnosis of JDM are associated with longer time to remission.[9] Cutaneous scarring or atrophy, resulting from long-lasting skin disease, are reported in 53% of patients.[23]

## Pulmonology

ILD is identified in 8% of patients with JDM.[29] Although it is often asymptomatic, the assessment is important because ILD is a significant cause of morbidity and mortality.[9] Serum Krebs von den Lungen-6 and ferritin levels are elevated in JDM patients with ILD, and these may be early markers.[1] The correlation between Krebs von den Lungen-6 and IL-18 suggests that alveolar macrophages may be associated with ILD pathogenesis.[30] There are ethnic differences in the relationship between anti-MDA5 autoantibody and ILD, with 9% (21/242) of patients with JDM having anti-MDA5 autoantibodies in the UK[20] and 41% (18/44) in Japan.[30] In anti-MDA5 antibody-positive patients with JDM, 19% (4/21) have ILD in UK, and 100% (18/18) in Japan. Moreover, in JDM patients with rapidly progressive ILD, no patients having anti-MDA5 antibodies were observed in the UK, whereas all patients have them in Japan. Further studies are needed to clarify these ethnic differences. Although anti-aminoacyl transfer ribonucleic acid synthetase (ARS) antibodies are rare in JDM patients, 63% of juvenile idiopathic inflammatory myopathies patients with these autoantibodies have ILD.[31] These patients have high mortality rates owing to ILD. Spontaneous pneumothorax and pneumomediastinum rarely occur, likely owing to vasculopathy.[32] All patients with JDM should undergo pulmonary function tests, including carbon monoxide diffusing capacity, at the time of diagnosis.[9] A regular assessment of pulmonary function may be prudent in patients with anti-MDA 5 and anti-ARS antibodies.[33]

## Cardiology

Patients with JDM have increased prevalence of electrocardiogram abnormalities and reduced heart rate variability.[34] Pericarditis and myocarditis have also been reported. Long-axis strain and the ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity are markers for systolic and diastolic involvement on echocardiograms.[5] Although most patients are asymptomatic, systolic and diastolic dysfunction is detected by echocardiography in patients with high early skin disease activity.[35] Vasculopathy in the myocardium may resemble vasculopathy in the skin. Cardiorespiratory fitness was found to be lower in patients with JDM, both with active and inactive disease, compared with controls after a mean 20 years of disease duration.[36] Electrocardiogram and echocardiography are recommended for all patients with JDM.[9]

## Hematology

Patients with JDM-associated macrophage activation syndrome (MAS) have occasionally been reported.[37] Four boys and two girls, the median age of whom was 12 years, ranging between 4 and 14, were studied. All six patients survived JDM-associated MAS after immunosuppressive therapy, although systemic juvenile idiopathic arthritis-associated MAS is a life-threatening condition; the mortality rates reach 20%.[38] Distinct changes in IL-6 and IL-18 levels during treatment may indicate the unique pathophysiology of JDM-driven complications. JDM has not been generally associated with the development of malignant neoplasms.[39]

## Gastroenterology

Ulceration and perforation can occur in any part of the gastrointestinal tract,[1] although these reports are old and should be replicated. Nonetheless, assessment is important because it can be a cause of mortality.

## Endocrinology

Growth failure is a feature of cumulative damage in JDM and occurs in around 10% of patients.[5] Patients with lipodystrophy have increased risk of hypertriglyceridemia, insulin resistance, and diabetes.[40] In such cases, cooperation of registered dietitians is necessary. Using GC can affect the hypothalamus-pituitary-adrenal axis in patients.

## Ophthalmology

Chorioretinopathy is a rare finding in JDM.[41] Although patients with JDM do not usually warrant ophthalmologic examinations, any patient with visual symptoms should have a careful dilated examination for retinopathy or GC-induced cataracts. GC treatment may lead to ocular complications, and the occurrence of ocular hypertension may be related to

GC susceptibility. Therefore, regular eye monitoring is important for the patients suffering from JDM.

## Psychology

In JDM, disease activity may affect school attendance, exam performance, and disrupt friendships.[5] On the other hand, using GC can lead to psychotic symptoms. Without adequate support, this may limit educational and career prospects, impair the ability to form social relationships, and damage self-esteem. Moreover, not only patients, but also their siblings and parents, are vulnerable to psychological distress, and could benefit from psychosocial assessments and interventions at disease onset and throughout its course.[42] Thus, many pediatric rheumatology services have engaged dedicated psychologists and social workers for addressing this issue.

## Radiology

Magnetic resonance imaging (MRI) is a sensitive and reliable method for detecting and quantifying muscle inflammation at the time of diagnosis in JDM.[43] In addition, it can help differentiate between active and inactive disease during follow-up. A muscle MRI facilitates objective assessments of JDM flares. MRI findings of subcutaneous fat involvement are characteristic of early-diagnosed JDM and correlates with elevated serum aldolase.[44] MRI has also been suggested to be useful in confirming diagnosis of lipodystrophy or monitoring response to treatment strategies.[5] A whole body MRI scoring system for muscular, subcutaneous tissue, and myofascial abnormalities has revealed its immense ability to estimate the overall inflammatory burden and treatment-related changes.[45]

Ultrasonography is a useful tool for myositis.[46] When MRI or muscle biopsy is unavailable, muscle ultrasonography can be an alternative to assess myositis activity.[9]

Actively exploring calcinosis by manual palpation and plain radiographs is highly recommended, whereas computed tomography (CT) has shown no additional benefits over radiographs for the detection of calcinosis in JDM.[47] On the other hand, patients with JDM should undergo high-resolution CT when restrictive pulmonary disease is present;[9] however, the risk of radiation associated with repeated CT must be considered.[48]

## Therapeutics

### Pharmacology

GC remains the first-line treatment for JDM, followed by GC-sparing agents. The prognosis of JDM has significantly improved over the last few decades owing to the use of GC[16]. Early aggressive treatment is reported to improve the long-term outcome. Methotrexate (MTX) also remains an important therapy for JDM and is used extensively both as mono- and combination therapy.[49] Approximately 70% of patients with JDM benefit significantly from MTX therapy. Cyclosporine A (CsA), tacrolimus, or azathioprine may also be used, if MTX is not tolerated. In refractory cases, intravenous immunoglobulin[9] can be added as a second-line treatment. Mycophenolate mofetil[50,51] may be a second- or third-line agent before using cyclophosphamide (CPA), because of fewer side effects. CPA[52] is emerging as a third-line agent in more severe or refractory cases.

Rituximab, abatacept, adalimumab, infliximab, or tocilizumab are treatment options for refractory JDM.[16,53,54] However, TNF inhibitors may be contraindicated because of worsening of radiological and clinical symptoms and the activation of the type I IFN system in several cases of adult refractory idiopathic inflammatory myopathies.[55] Further prospective studies are needed to explore the potential safety and efficacy of Janus kinase inhibitors in JDM, not only for refractory cases, but also as a first-line treatment.[56] In rapidly progressive ILD, a combination therapy of methylprednisolone pulse therapy, CsA, and CPA can be administered. Liposteroid, a lipid emulsion containing dexamethasone, provides greater efficacy, and much less risk for systemic adverse effects than dexamethasone sodium phosphate.[57] Liposteroid has been effectively used for the treatment of macrophage activation syndrome in Japan, because lipid emulsions are easily taken up by phagocytosis and are retained in macrophages. Liposteroid (intravenous dexamethasone palmitate: 10 mg/$m^2$/day as dexamethasone in two divided doses) with CsA is one of the preferred treatment options for pediatric MAS,[37,58,59] including JDM-associated MAS.[60] The risk of posterior reversible encephalopathy syndrome is presumably lower under liposteroid therapy compared with methylprednisolone pulse therapy.[57]

### Physiotherapy

Exercise has been suggested to relieve chronic systemic inflammation in patients with JDM.[61] It has been shown that expression of genes involved in disease activity and inflammation is decreased by exercise, and it is further reported that mitochondrial enzyme activity is increased and muscle oxygen consumption is improved.[62] In exercise therapy for myositis, both intensive aerobic and weight training have been postulated to reduce myopathic disease activity and inflammation and improve muscle

metabolism.[63] A 12-week home-based exercise program was safe, and led to significant improvement in long jump distance, 30-s push-ups and sit-ups, and the child health assessment questionnaire score completed by parents.[64] Using myometry and MRI, and measuring serum creatine kinase and lactate dehydrogenase levels, exercise was not found to increase muscle inflammation.[5]

### Stem cell transplantation

Autologous hematopoietic stem cell transplantation might be safe and effective in treating refractory JDM, and can provide long-term drug-free survival.[65] However, this remains to be confirmed in studies with larger populations.

### Surgery

Surgical resection may be a candidate treatment for established calcinosis[66] if drug therapy fails to control the disease. Aggressive biological treatments and timely surgical interventions are important in reducing mortality rate in gastrointestinal ulceration and perforation.[5]

## Preventive medicine

### Sunscreen

In patients with JDM, dermatitis is photosensitive, and ultraviolet (UV) light may increase the risk of recurrence. Sunscreen protection against both UV-A and -B wavelengths, with high sun-protection factors (SPF), are necessary.[1] The protection rate from UV radiation is approximately 93%, 97%, and 99% for SPF 15, 30, and 70, respectively. Photosensitivity often necessitates use of SPF 70 or higher, although a recent international upper limit allows the display of SPF 70 as 50+. Thus, using SPF 50+ is desirable. On the other hand, a recent study in a large cohort of patients with JDM reported an association between UV radiation, calcinosis, and ethnicity; with increasing UV radiation, the probability of calcinosis markedly decreased in black subjects and steadily increased in non-black subjects.[67] Thus, the indication of sunscreen use in JDM patients might be carefully considered.

### Vaccination

Although inactivated vaccines are considered safe,[68] the antibody titers after vaccination are lower in patients with JDM than in healthy children.[69] There is little knowledge about the safety of live-attenuated vaccines for patients with JDM treated with GC and immunosuppressants.

## Adult rheumatology

### Relationship between juvenile and adult dermatomyositis

Similarities and differences between JDM and adult dermatomyositis (ADM) have been reported.[1] For example, vasculopathy, calcinosis, and skin ulceration are more pronounced in JDM than in ADM. Conversely, there is less chance of ILD and the development of malignant neoplasms in JDM than in ADM. Moreover, patients with JDM have a better life prognosis than those with ADM. In MSAs of ADM, anti-ARS antibodies are common, and anti-TIF1-γ antibody is associated with malignant neoplasms.

### Transitional care

Considering the management of transitional care, it is crucial to construct a system that provides whole-person care to every patient by coordinating between the departments of pediatric rheumatology and adult rheumatology.[70] In addition, basic and clinical studies evaluating long-term clinical course of JDM and the difference between pediatric and adult onset diseases are necessary. These efforts may contribute to the development of better treatment strategies in the future.

## Summary

Juvenile dermatomyositis (JDM) is strongly associated with immune-related genes of human leukocyte antigen region. Characteristic abnormalities include excess type I interferon production in blood and muscles, leading to immune cell activation and vasculopathy. The most common myositis-specific autoantibodies in JDM are anti-transcription intermediary factor 1-γ and anti-nuclear matrix protein 2. The severity of histological changes from muscle biopsy is closely correlated with myositis-specific autoantibodies. Magnetic resonance imaging is a sensitive and reliable method for detecting and quantifying muscle inflammation; muscle strength may be tested using the childhood myositis assessment scale or manual muscle test. Nailfold capillary changes also provide a sensitive measure of disease activity. Interstitial lung disease and gastrointestinal ulceration assessment, electrocardiogram, and echocardiography are indicated for all children with JDM. Growth failure is also a key feature of cumulative damage in JDM. Regular eye monitoring is important for children suffering from JDM. Children with JDM, siblings, and parents are vulnerable to psychological distress, and could benefit from psychosocial assessments and interventions. Glucocorticoid remains the first-line

treatment in this regard, followed by methotrexate, and mycophenolate mofetil and biologic agents can treat refractory cases. Children reported with JDM-associated macrophage activation syndrome survived after immunosuppressive therapy. Exercise can relieve chronic systemic inflammation, and established calcinosis might respond to surgical resection. Sunscreen protection against ultraviolet light is generally necessary. Management of transitional care by coordinating between pediatric and adult rheumatologists is essential. Furthermore, updates on epidemiology are also important. Overall, for the elucidation of JDM pathophysiology and establishment of appropriate treatment for children with JDM, more extensive multispecialty collaborations are warranted.

## Disclosure

The author reports no conflicts of interest in this work.

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