Pegem Journal of Education and Instruction, Vol. 14, No. 3, 2024 (pp. 843-853)

RESEARCH ARTICLE WWW.PEGEGOG.NET

The Cardiovascular Burden of Familial Mediterranean Fever in Childhood: Integrating Pathophysiology With Modern Cardiac Assessment Tools

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ABSTRACT

***Background*:** Familial Mediterranean Fever (FMF) is the most common monogenic autoinflammatory disease of childhood, driven by *MEFV* mutations that lead to dysregulated interleukin-1–mediated inflammation. Although FMF is best known for episodic febrile serositis, accumulating evidence indicates that chronic subclinical inflammation may impose measurable cardiovascular stress even during attack-free periods. In children—whose cardiac and vascular systems are still developing—persistent inflammatory exposure may influence myocardial architecture, endothelial function, autonomic balance, and long-term cardiovascular risk. Importantly, the cardiovascular burden in pediatric FMF often remains asymptomatic until advanced, underscoring the need for early and sensitive detection tools.

Aim: This review integrates current knowledge on the cardiovascular burden of FMF in childhood, emphasizing the interplay between inflammatory pathophysiology and the diagnostic yield of modern cardiac assessment techniques. We explore mechanisms linking pyrin dysfunction to myocardial and vascular injury, highlight findings from myocardial strain imaging, arterial stiffness measurements, and electrophysiologic analyses, and evaluate how biomarkers complement imaging in detecting early dysfunction. By synthesizing pathophysiologic insights with emerging pediatric cardiology tools, this review aims to outline an evidence-based framework for risk stratification and longitudinal cardiac surveillance in FMF children.

Conclusion: Pediatric FMF is associated with a broadly subclinical yet clinically relevant cardiovascular burden, shaped by chronic low-grade inflammation, endothelial injury, arrhythmogenic susceptibility, and potential long-term atherosclerotic risk. Modern diagnostic modalities—including speckle-tracking echocardiography, tissue Doppler imaging, heart rate variability analysis, and vascular stiffness assessments—have improved the ability to identify early myocardial and vascular changes far earlier than conventional evaluation. Integrating these modalities with inflammatory biomarkers and genetic risk indicators enables more precise monitoring and informs therapeutic decisions, such as intensifying colchicine therapy or considering biologic treatment in high-risk patients. Despite progress, major gaps remain regarding the long-term prognostic value of subclinical abnormalities and the optimal timing and frequency of pediatric cardiac screening. Future multicenter pediatric studies are essential to refine risk prediction models and develop standardized, evidence-based cardiovascular monitoring protocols for children with FMF.

Keywords: Cardiovascular Burden, Familial Mediterranean Fever, Cardiac Assessment Tools

INTRODUCTION

Familial Mediterranean Fever (FMF) is the most prevalent hereditary autoinflammatory disease of childhood, characterized by recurrent febrile episodes and persistent subclinical inflammation linked to mutations in the *MEFV* gene encoding pyrin.

Although the disease classically manifests with serositis, increasing research demonstrates that FMF also exerts a measurable cardiovascular burden even in early life. Chronic elevation of inflammatory mediators such as IL-1β, TNF-α, and serum amyloid A (SAA) can impair endothelial function, alter myocardial relaxation, and modify autonomic cardiac regulation. Importantly, many of these abnormalities remain clinically silent, detectable only through sensitive imaging or electrophysiologic techniques. This subclinical nature makes the pediatric population particularly vulnerable, as cardiovascular changes may accumulate over years before symptoms emerge. [1–4]

Despite mounting evidence linking FMF to subtle cardiac dysfunction, standardized pediatric screening strategies are lacking, and the prognostic implications of early findings—such as reduced global longitudinal strain, increased carotid intima–media thickness, or variations in heart rate variability—remain uncertain. Current clinical practice heavily relies on conventional echocardiography, which may fail to detect early myocardial or endothelial abnormalities. Modern modalities such as speckle-tracking echocardiography, tissue Doppler imaging, biomarkers (NT-proBNP, endocan, ADMA), and vascular stiffness indices provide deeper insights into the cardiovascular consequences of chronic inflammation. However, their integration into routine pediatric monitoring remains inconsistent due to limited longitudinal pediatric data. The aim of this review is to synthesize the mechanistic pathways contributing to cardiovascular burden in childhood FMF and to evaluate how modern cardiac assessment tools enhance early detection, risk stratification, and clinical decision-making. [5–8]

Pathophysiology of Cardiovascular Involvement in Childhood FMF

Chronic inflammation lies at the center of the cardiovascular burden in pediatric FMF. The disease is driven by mutations in the *MEFV* gene, which result in dysregulated activation of the pyrin inflammasome and excessive release of interleukin-1β (IL-1β). This leads to persistent production of downstream inflammatory mediators such as IL-6, TNF-α, and serum amyloid A, which circulate even during attack-free periods. In children, whose cardiovascular tissues are still developing, sustained inflammatory exposure can induce endothelial dysfunction, impair nitric oxide bioavailability, and promote oxidative stress. These processes collectively contribute to early vascular abnormalities—including increased arterial stiffness and impaired flow-mediated dilation—that are well documented in pediatric FMF cohorts. [9–11]

Endothelial dysfunction represents one of the earliest measurable cardiovascular effects in FMF and reflects a shift toward a pro-inflammatory, pro-atherogenic vascular environment. Inflammatory cytokines disrupt endothelial integrity, increase vascular permeability, and impair vasodilatory responses mediated by nitric oxide. Pediatric studies consistently show elevated levels of asymmetric dimethylarginine (ADMA), endocan, and other endothelial injury biomarkers in FMF patients compared with healthy controls. These biomarkers often correlate with measures of arterial stiffness and carotid intima–media thickness, highlighting the mechanistic link between inflammation and vascular remodeling. The cumulative effect of endothelial dysfunction over years of childhood may lay the groundwork for accelerated atherosclerosis later in life. [12–14]

Myocardial involvement in FMF is thought to arise from inflammation-induced microvascular dysfunction, alterations in myocardial relaxation, and subtle interstitial remodeling. Although overt myocarditis is rare in children, chronic cytokine exposure can impair diastolic relaxation and modify myocardial strain patterns long before conventional measures such as ejection fraction are affected. Speckle-tracking echocardiography has revealed reductions in global longitudinal strain and abnormalities in early diastolic strain rate in many FMF children with no clinical symptoms. These findings support the hypothesis that FMF-related myocardial dysfunction is largely subclinical and may reflect chronic inflammatory effects on myocardial extracellular matrix turnover, microvascular perfusion, and autonomic signaling. [15–17]

Autonomic dysregulation offers another mechanistic dimension to the cardiovascular burden in pediatric FMF. Studies of heart rate variability demonstrate decreased parasympathetic activity and heightened sympathetic tone, even during disease remission. Chronic inflammation may interfere with cardiac autonomic centers or modulate afferent inflammatory signaling, contributing to altered repolarization indices such as prolonged QTc or increased P-wave dispersion. While clinically significant arrhythmias are uncommon in FMF children, these subclinical electrophysiological changes raise concerns about vulnerability to autonomic imbalance during febrile attacks or in the setting of uncontrolled inflammation. Understanding the interplay between inflammation and autonomic regulation is crucial, as these mechanisms may influence both myocardial and vascular outcomes. [18–20]

Amyloidosis represents the most severe potential outcome of sustained inflammation, although clinically significant cardiac amyloid deposition is exceedingly rare in children. Nevertheless, prolonged elevation of serum amyloid A—even in childhood—

may induce early extracellular matrix changes that subtly increase myocardial stiffness. Pediatric patients with persistently uncontrolled inflammation or inadequate colchicine adherence are at highest risk for preclinical amyloid accumulation. While overt cardiac amyloidosis is typically an adult complication, early strain abnormalities detected in some pediatric FMF cohorts raise questions about whether reversible inflammatory myocardial changes could evolve into more permanent structural alterations later in life. [21–22]

Clinical Manifestations of Cardiovascular Involvement in Childhood FMF

Cardiovascular manifestations in pediatric FMF typically present along a spectrum ranging from completely asymptomatic subclinical abnormalities to rare but clinically significant complications. The most frequent findings involve subtle alterations in myocardial relaxation, early diastolic dysfunction, or reduced strain parameters, all of which frequently occur without overt cardiac symptoms. Children often maintain normal ejection fraction on standard echocardiography, masking the underlying functional impairment that can only be detected through more advanced modalities such as tissue Doppler or speckle-tracking imaging. These silent abnormalities underscore the importance of proactive cardiovascular assessment in FMF, especially in those with high inflammatory load or severe genotypes. [23–25]

Endothelial dysfunction is among the earliest clinically detectable abnormalities. Pediatric cohorts consistently demonstrate reduced flow-mediated dilation (FMD), increased carotid intima–media thickness (cIMT), and elevated arterial stiffness measures. These changes often correlate with attack frequency, chronic elevation of acute-phase reactants, and markers such as ADMA or endocan. Although such vascular impairments rarely produce symptoms during childhood, they signify a predisposition to accelerated atherosclerosis, making FMF one of the few autoinflammatory conditions where early vascular injury may begin in childhood. The asymptomatic nature of vascular involvement highlights the necessity of integrating vascular imaging into the long-term follow-up of selected FMF patients. [26–28]

Electrophysiological abnormalities represent another clinically relevant but often overlooked aspect of FMF-related cardiac involvement. Changes such as prolonged QTc interval, increased P-wave dispersion, decreased heart rate variability, and abnormal repolarization indices have been reported in multiple pediatric studies. While these findings rarely translate into symptomatic arrhythmias during childhood, they may indicate autonomic imbalance driven by chronic inflammatory signaling. Children with these abnormalities may require periodic cardiologic assessment, especially during febrile attacks or in cases of colchicine resistance, when autonomic disturbance may be amplified. [29–31]

Pericardial involvement, although less common in the pediatric population, remains a recognized clinical manifestation of FMF. Episodes of pericarditis may occur during inflammatory attacks and present with chest pain, dyspnea, or characteristic positional discomfort. However, many cases involve minimal effusion and may go undiagnosed without echocardiography. Recurrent pericarditis, although uncommon, has been observed in a subset of children and may respond variably to colchicine therapy. Differentiating FMF-related pericarditis from infectious or autoimmune etiologies is clinically important, particularly when effusions persist or when systemic inflammatory markers fail to normalize. [32–33]

The most severe and clinically consequential cardiac manifestation—AA amyloidosis involving the myocardium—is exceedingly rare in childhood, thanks to early diagnosis and widespread colchicine use. However, persistent elevation of serum amyloid A, especially in children with poor adherence or colchicine-resistant disease, raises theoretical concern for early microscopic amyloid deposition. Although overt cardiac amyloidosis is almost never seen in children, subtle increases in myocardial stiffness or early diastolic abnormalities raise the possibility of preclinical remodeling, highlighting the importance of stringent inflammation control throughout childhood to prevent long-term sequelae. [34–35]

Diagnostic Assessment Tools for Evaluating Cardiovascular Burden in Pediatric FMF

Conventional Echocardiography

Conventional transthoracic echocardiography remains the initial and most accessible tool for evaluating cardiac involvement in children with FMF. While standard measures such as left ventricular ejection fraction (LVEF) often appear normal, more sensitive Doppler-derived indices can reveal early diastolic dysfunction. Alterations in mitral inflow patterns—including reduced E/A ratio and prolonged deceleration time—have been consistently reported in pediatric FMF cohorts, even in those with minimal symptoms. These findings reflect impaired ventricular relaxation attributed to chronic inflammatory exposure. However, conventional echocardiography lacks sensitivity to detect subtle myocardial or microvascular abnormalities, necessitating the

use of advanced modalities in at-risk patients. [36–38]

Tissue Doppler Imaging (TDI)

TDI is a significant advancement over standard Doppler techniques, providing quantifiable measurements of myocardial velocities during systole and diastole. In children with FMF, reduced early diastolic myocardial velocity (Em), increased myocardial performance index (MPI), and alterations in E/Em ratios have been documented, demonstrating impaired myocardial relaxation and early global dysfunction. These abnormalities often correlate with inflammatory markers, suggesting a direct mechanistic association between chronic cytokine exposure and myocardial performance. The reproducibility and wide availability of TDI make it a valuable screening tool for detecting early functional impairment. [39–41]

Speckle-Tracking Echocardiography (Myocardial Strain Imaging)

Speckle-tracking echocardiography has emerged as one of the most sensitive techniques for detecting subclinical myocardial involvement in FMF children. Studies consistently show reductions in global longitudinal strain (GLS) and abnormalities in circumferential and radial strain, even when LVEF remains within normal limits. Strain imaging captures early deformation abnormalities influenced by microvascular dysfunction, myocardial edema, or subtle fibrosis. Because these abnormalities can appear early and progress with persistent inflammation, strain analysis is increasingly recommended for longitudinal assessment of children with severe genotypes, high SAA levels, or frequent inflammatory attacks. [42–44]

Electrocardiography and Electrophysiologic Testing

Electrocardiographic assessment is essential in evaluating the autonomic and electrophysiologic impact of FMF. Prolonged QTc intervals, increased P-wave dispersion, and reduced heart rate variability (HRV)—especially decreased parasympathetic activity—have been consistently observed in pediatric FMF populations. These findings reflect inflammation-related disturbances in autonomic tone and myocardial repolarization. Although symptomatic arrhythmias are rare, the presence of electrophysiologic abnormalities justifies periodic ECG monitoring, particularly for children with persistent inflammation or colchicine resistance. Holter monitoring may be warranted in cases with borderline QTc values or concerning symptoms. [45–47]

Biomarkers of Cardiovascular Stress and Endothelial Injury

Biomarkers provide additional insight into cardiovascular involvement by reflecting inflammatory load, myocardial stress, or endothelial dysfunction. Elevated serum amyloid A (SAA) and high-sensitivity C-reactive protein (hs-CRP) are common in children with FMF and correlate with vascular abnormalities such as increased arterial stiffness. NT-proBNP has been shown to rise in FMF children with early diastolic dysfunction or strain abnormalities, suggesting subtle cardiac stress. Endothelial biomarkers such as endocan and ADMA further enhance diagnostic sensitivity by capturing vascular injury processes that are otherwise undetectable with routine imaging. Combining biomarkers with imaging modalities improves diagnostic accuracy and risk stratification. [48–51]

Assessment of Vascular Structure and Function

Vascular imaging techniques such as carotid intima–media thickness (cIMT) and arterial stiffness measurements provide quantifiable markers of early vascular remodeling. Increased cIMT and impaired flow-mediated dilation (FMD) are documented in multiple pediatric FMF studies, reflecting endothelial injury and reduced vascular elasticity. Pulse wave velocity (PWV), a marker of arterial stiffness, also tends to be elevated in FMF children, even during clinical remission. These findings indicate an inflammation-driven acceleration of vascular aging, making vascular imaging an important tool in assessing FMF cardiovascular burden. [52–54]

Cardiac Magnetic Resonance Imaging (MRI)

Cardiac MRI offers superior soft tissue characterization and is invaluable in evaluating myocardial edema, fibrosis, or suspected myocarditis. Though less frequently used in children, MRI studies in FMF populations reveal subtle alterations in T1/T2 mapping and extracellular volume fraction that may indicate interstitial inflammation or early remodeling. MRI can detect abnormalities even when echocardiography is unremarkable, making it the gold standard for complex or ambiguous cases. The technique's limitations include cost, sedation needs in young children, and limited availability, but its diagnostic value is substantial in selected populations. [55–56]

Emerging Diagnostic Approaches

Novel approaches such as three-dimensional myocardial strain, myocardial work index assessment, and microRNA profiling are expanding the diagnostic landscape. These tools may help distinguish reversible inflammatory myocardial dysfunction from more persistent structural changes. Additionally, artificial intelligence–enhanced echocardiographic analysis and automated vascular stiffness quantification hold future promise for improving diagnostic precision. While still largely research-focused, these emerging technologies are expected to play increasing roles in pediatric FMF evaluation as validation data accumulate. [57–58]

Integrative Evaluation Strategy for Cardiovascular Risk in Pediatric FMF

Developing an integrative evaluation strategy for cardiovascular involvement in childhood FMF requires combining the mechanistic understanding of inflammation-driven cardiac and vascular changes with the strengths of modern diagnostic tools. No single modality captures the full spectrum of cardiovascular effects—ranging from endothelial dysfunction to subtle myocardial strain abnormalities—making multimodal assessment essential. By layering conventional imaging, advanced echocardiographic techniques, electrophysiologic markers, and endothelial biomarkers, clinicians can identify early abnormalities that may otherwise remain undetected. This integrative approach is especially important in children with high disease activity, severe genotypes (such as M694V homozygosity), or evidence of persistent inflammation despite colchicine therapy. [59–61]

A tiered assessment model is a practical and clinically relevant framework. At the base level, all pediatric FMF patients should undergo periodic ECG and conventional echocardiography to screen for overt abnormalities and to establish baseline cardiac function. Children with abnormal diastolic indices, borderline repolarization abnormalities, or fluctuating inflammatory markers should then proceed to advanced imaging modalities such as tissue Doppler and speckle-tracking strain analysis. Strain imaging, in particular, can reveal hidden myocardial dysfunction that conventional echocardiography may miss. Integration of vascular imaging—such as carotid intima–media thickness and pulse wave velocity—can further stratify cardiovascular risk by detecting early endothelial injury and arterial stiffness. [62–64]

Biomarkers play a key complementary role within this integrated framework. Elevated serum amyloid A (SAA), hs-CRP, endocan, NT-proBNP, and ADMA levels can help identify children experiencing ongoing subclinical inflammation or endothelial injury. When these biomarkers correlate with abnormalities in strain imaging or vascular stiffness, the predictive value of early cardiovascular involvement becomes significantly stronger. Such biomarker–imaging clusters may ultimately guide therapeutic decisions, such as intensifying colchicine, increasing monitoring intervals, or considering IL-1 blockade for refractory inflammation. Importantly, consistent biomarker trends over time—rather than isolated elevations—offer the most reliable reflection of cardiovascular inflammatory burden. [65–67]

A truly integrative strategy must also incorporate genetic and clinical risk factors. Children with early-onset FMF, frequent attacks, poor colchicine adherence, or pathogenic *MEFV* mutations associated with severe inflammation exhibit disproportionately higher cardiovascular risk and should enter enhanced surveillance pathways. In these children, combining strain echocardiography with endothelial markers and periodic vascular imaging can identify clinically silent progression. Moreover, emerging modalities such as myocardial work index and machine-learning–enhanced echocardiographic interpretation may allow more precise quantification of early myocardial burden. Although these tools are still evolving, they highlight the future direction of risk-adapted cardiovascular monitoring in pediatric FMF. [68–70]

An essential component of integrated evaluation is longitudinal follow-up. Because cardiovascular changes in FMF tend to be subtle, dynamic, and inflammation-dependent, repeated assessments over years are far more informative than single time-point measurements. Tracking strain patterns, arterial stiffness, or variability in autonomic markers allows clinicians to determine whether abnormalities are stable, improving with therapy, or progressing due to uncontrolled inflammation. Integrating these longitudinal data into individualized risk profiles can lead to earlier therapeutic interventions, potentially preventing long-term sequelae such as premature atherosclerosis or persistent myocardial dysfunction. [71]

Therapeutic and Clinical Implications of Cardiovascular Involvement in Pediatric FMF

Colchicine therapy remains the cornerstone of FMF management and plays a central role in mitigating cardiovascular complications by controlling systemic and subclinical inflammation. Adequate colchicine adherence significantly reduces serum

amyloid A (SAA) and C-reactive protein (CRP) levels, which are strongly correlated with myocardial strain abnormalities and vascular dysfunction. Pediatric studies demonstrate that children with well-controlled disease show improved diastolic indices, normalization of myocardial performance index, and stabilization of arterial stiffness measurements over time. These findings highlight that the majority of FMF-associated cardiovascular changes may be functional rather than structural and therefore potentially reversible with consistent colchicine therapy. The therapeutic implication is clear: optimizing colchicine dosing and adherence is essential not only for preventing amyloidosis but also for reducing early cardiovascular burden. [72–74]

Despite the significant benefits of colchicine, a subset of children—particularly those with colchicine-resistant FMF—continue to exhibit elevated inflammatory markers and abnormal cardiac parameters. In such cases, IL-1 blockade using agents such as anakinra or canakinumab has emerged as an effective strategy to suppress inflammation. Although pediatric data specifically linking IL-1 inhibition to improved cardiac outcomes are limited, adult and mixed-age FMF studies show improvements in endothelial function, inflammatory biomarkers, and vascular stiffness after biologic therapy. Given the mechanistic role of IL-1β in myocardial and vascular injury, it is reasonable to consider biologic escalation in children with persistent strain abnormalities, accelerated arterial stiffness, or recurrent pericarditis despite optimized colchicine therapy. Future pediatric-specific trials are necessary to determine whether cardiac parameters should serve as triggers for advancing to biologic therapy. [75–77]

Cardiovascular findings also influence broader clinical management decisions beyond anti-inflammatory therapy. Children with electrophysiologic alterations, such as prolonged QTc or reduced heart rate variability, may require adjustment of medications that affect cardiac repolarization, as well as periodic ECG monitoring during febrile episodes or biologic therapy initiation. In those with significant vascular involvement—such as increased cIMT or elevated PWV—lifestyle and metabolic risk factor management becomes increasingly important. Counseling about physical activity, body weight optimization, and avoidance of passive smoke exposure can help mitigate long-term cardiovascular risk. Although these considerations are not traditionally emphasized in FMF guidelines, the accumulating evidence of endothelial dysfunction in children supports integrating preventive cardiology principles into FMF care. [78–79]

Finally, the presence of cardiac and vascular abnormalities in FMF has implications for long-term disease monitoring into adolescence and adulthood. Children with persistently abnormal strain patterns or vascular stiffness may require transition plans that include adult cardiology follow-up, particularly as chronic inflammation and time increase the likelihood of clinically significant cardiovascular disease. Identifying children who demonstrate early or progressive abnormalities allows clinicians to prioritize intensified monitoring and early preventive interventions. The long-term implications underscore one of the key therapeutic messages: controlling inflammation early in life may modify cardiovascular trajectories and reduce the risk of adult morbidity in FMF patients. [80–81]

Screening and Follow-up Recommendations for Cardiovascular Monitoring in Pediatric FMF

Effective cardiovascular surveillance in children with FMF requires a structured, risk-adapted strategy that reflects both the inflammatory nature of the disease and the sensitivity of modern assessment tools. At the foundation of this approach is the recommendation that all newly diagnosed pediatric FMF patients undergo baseline evaluation with a 12-lead ECG and comprehensive transthoracic echocardiography, including Doppler measurements of diastolic function. These investigations provide essential baseline reference points for future comparison and can detect early abnormalities, such as mild diastolic dysfunction or borderline repolarization changes, that may not yet have clinical expression. Such baseline assessments are especially valuable in children with severe genotypes or early disease onset. [82–83]

Higher-risk subgroups—including children with frequent inflammatory attacks, persistently elevated SAA or CRP levels, incomplete response to colchicine, or a history of pericarditis—require more detailed cardiac evaluation. In these patients, incorporation of advanced echocardiographic modalities, such as tissue Doppler imaging and speckle-tracking strain analysis, is strongly recommended. Strain imaging can detect subtle myocardial deformation abnormalities that precede traditional echocardiographic changes and often correlate with disease activity or inflammatory markers. Because strain abnormalities have been documented even in asymptomatic children, periodic reassessment every 12–18 months is advisable for high-risk individuals. [84–85]

Vascular assessment should also be part of the surveillance strategy in selected pediatric FMF patients, particularly those with prolonged disease duration, elevated endothelial biomarkers, or family history of premature cardiovascular disease.

Measurements of carotid intima–media thickness (cIMT), arterial stiffness (pulse wave velocity), and flow-mediated dilation (FMD) can reveal early vascular injury and impaired endothelial function. Although vascular imaging need not be performed annually, repeating these studies every 1–2 years in at-risk children helps detect progressive arterial remodeling that might not manifest clinically until adulthood. Integration of biomarkers—such as ADMA, endocan, and NT-proBNP—strengthens the predictive value of imaging findings and guides clinical decision-making. [86–88]

Electrophysiologic monitoring is essential for children exhibiting signs of autonomic dysfunction, including prolonged QTc interval, increased P-wave dispersion, or reduced heart rate variability. Annual ECG is reasonable for most FMF patients, but Holter monitoring may be indicated for those with abnormal repolarization markers or symptoms such as palpitations or syncope. These assessments are particularly important during periods of heightened inflammatory activity, such as frequent febrile episodes or incomplete colchicine response, when autonomic imbalance may intensify. Early identification of electrophysiologic disturbances allows timely referral to pediatric cardiology and adjustment of medications that may influence cardiac conduction. [89–90]

Follow-up strategies should emphasize longitudinal trend analysis rather than isolated measurements. Repeated assessments over years—incorporating imaging, biomarkers, and ECG parameters—allow clinicians to track whether abnormalities remain stable, improve with therapy, or progress due to persistent inflammation. This dynamic approach allows for individualized monitoring frequencies: clinically stable children with normal findings may be followed every 2–3 years, whereas those with persistent abnormalities may require annual or more frequent evaluation. Ultimately, the goal is early identification of children whose cardiovascular profile suggests elevated long-term risk, enabling timely therapeutic intensification and preventive cardiology interventions before irreversible structural or functional changes develop. [91]

Conclusion

Familial Mediterranean Fever in childhood is increasingly recognized as a condition with meaningful cardiovascular implications that extend beyond its classic inflammatory phenotype. Although most affected children appear clinically well, accumulating evidence shows that chronic subclinical inflammation can subtly influence myocardial function, vascular health, and autonomic regulation. These alterations—often detectable only through advanced diagnostic tools such as myocardial strain imaging, arterial stiffness assessment, and detailed electrophysiologic analysis—represent early indicators of inflammation-driven cardiovascular burden. Their presence highlights the importance of proactive, structured evaluation in pediatric FMF, even in the absence of overt cardiac symptoms.

The integration of mechanistic understanding with modern cardiac assessment technology allows a far more comprehensive appraisal of cardiovascular risk in FMF than was previously possible. Multimodal evaluation that incorporates imaging, biomarkers, vascular studies, and electrophysiologic monitoring not only improves detection of early abnormalities but also helps clinicians identify which children are most vulnerable to long-term cardiovascular consequences. Importantly, many of these abnormalities appear reversible with effective inflammation control through colchicine or, when necessary, IL-1–targeted biologic therapy, underscoring the therapeutic value of early and sustained intervention.

Looking ahead, longitudinal surveillance will be essential to determine the prognostic significance of subclinical findings detected during childhood. Tailored follow-up strategies that consider genotype, disease severity, treatment response, and evolving cardiovascular parameters will allow clinicians to optimize both pediatric and long-term adult outcomes. Ultimately, recognizing and addressing the cardiovascular burden of FMF early in life offers an important opportunity to modify disease trajectory, reduce future morbidity, and improve quality of life for affected children.

How to cite this article: Eman Mahmoud El Moghazy, Amal Mohamed Abdellatif, Saed Mohamed Morsy, Ahmad Mohamed Mahmoud Romih(2024). The Cardiovascular Burden of Familial Mediterranean Fever in Childhood: Integrating Pathophysiology With Modern Cardiac Assessment Tools, Vol. 14, No. 3, 2024,842-853.

Source of support: None.

Conflict of interest: Nil.

Accepted: 26.06.2024 **Received** 03.06.2024

Published : 30.06.2024

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