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Physical Exercise as a Trigger and Therapeutic Tool in Mast Cell Activation Syndrome. A Narrative Literature Review of Mechanisms and Management Strategies

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Abstract

Background. Mast Cell Activation Syndrome (MCAS) is characterized by episodic, inappropriate release of mast cell mediators producing multisystem symptoms. Physical exercise acts both as a trigger for anaphylactic events and as a potential therapeutic modality in MCAS.

Aim. This review synthesizes evidence on MCAS pathophysiology, flare-up prevention strategies, and the bidirectional relationship between physical exercise and mast cell activation.

Material and methods. PubMed, Scopus, and Web of Science were searched using terms related to mast cell activation syndrome, exercise-induced anaphylaxis, and mast cell stabilization. Articles published between 1985 and 2025 were included, prioritizing consensus documents, systematic reviews, and original research.

Results. MCAS is classified into primary (clonal), secondary, and idiopathic forms, with diagnosis requiring multisystem symptoms, mediator elevation, and therapeutic response. Exercise triggers mast cell degranulation through osmolar, thermal, and neuroimmune mechanisms, yet structured moderate-intensity programs adapted from postural orthostatic tachycardia syndrome (POTS) rehabilitation protocols show benefit when combined with pharmacological premedication.

Conclusions. MCAS management in physically active individuals requires individualized trigger identification, stepwise pharmacotherapy, and graded exercise prescription.

Randomized trials of exercise protocols designed for MCAS populations remain an unmet research need.

Key words: mast cell activation syndrome, exercise-induced anaphylaxis, histamine, mast cell stabilizers, POTS, exercise intolerance, low-histamine diet, tryptase.

1. Introduction

Mast cells are among the oldest and most versatile effectors of the innate immune system. Derived from CD34-positive hematopoietic progenitors, they complete their differentiation in peripheral tissues under the influence of stem cell factor and its receptor KIT, and then persist for months to years at host-environment interfaces: the skin, gastrointestinal mucosa, airways, and perivascular and perineural spaces (Theoharides et al. 2015; 2019). Their granules contain a preformed arsenal of histamine, tryptase, heparin, and tumor necrosis factor alpha; upon activation, they also generate prostaglandin D2, leukotrienes C4/D4/E4, platelet-activating factor, and a broad cytokine repertoire including interleukins 1β, 6, 8, 13, and 33 (Valent et al. 2020). In health, this machinery underpins host defense, wound repair, and vascular homeostasis. When it misfires, repeatedly, excessively, and without commensurate provocation, the result is Mast Cell Activation Syndrome.

MCAS was first formalized as a diagnostic entity by Akin, Valent, and Metcalfe in 2010, who proposed three simultaneous criteria: episodic symptoms consistent with mast cell mediator release involving two or more organ systems; a documented rise in a validated mast cell mediator (most often serum tryptase) temporally linked to the symptomatic episode; and clinical improvement with mast-cell-directed pharmacotherapy (Akin et al. 2010). In the years that followed, competing diagnostic frameworks emerged. The Valent consensus criteria refined the tryptase threshold to a formula requiring a rise of at least 20% above baseline plus 2 ng/mL, establishing high specificity (Valent et al. 2019). A broader alternative, termed "Consensus-2," was championed by Afrin, Molderings, and colleagues, who substituted additional urinary mediator metabolites and relaxed the specificity requirements, arguing that serum tryptase alone misses a large fraction of patients with non-tryptase-predominant mediator profiles (Afrin et al. 2021). This disagreement is not merely academic; prevalence estimates swing from under 1% with strict Valent criteria to roughly 17% under Molderings'

extrapolations from a German family study, a figure that has attracted considerable skepticism (Molderings et al. 2013; Valent et al. 2022).

Clinically, MCAS spans dermatological symptoms (flushing, urticaria, angioedema), cardiovascular instability (hypotension, tachycardia, presyncope), gastrointestinal distress (cramping, diarrhoea, nausea), respiratory compromise (bronchospasm, nasal congestion), and neuropsychiatric features (brain fog, anxiety, headache). This polymorbidity overlaps extensively with other conditions (irritable bowel syndrome, chronic fatigue, fibromyalgia), making differential diagnosis difficult and fuelling ongoing debate about diagnostic boundaries (Theoharides et al. 2019; Giannetti et al. 2020).

A recurring clinical observation is the co-occurrence of MCAS with hypermobile Ehlers-Danlos syndrome (hEDS) and postural orthostatic tachycardia syndrome (POTS), a clustering sometimes called the "triad." Kohn and Chang's 2020 systematic review found the evidence base surprisingly thin: only four original research papers addressed the triad directly, and none established a unified pathomechanism (Kohn and Chang 2020). A more recent retrospective analysis by Yao and colleagues highlighted the definitional problem: among 100 consecutive POTS patients, 37% met Consensus-2 MCAS criteria while only 2% met the strict Valent criteria (Yao et al. 2025).

Physical exercise sits at the center of a paradox in MCAS. On one hand, exercise is a well-documented trigger for mast cell degranulation, capable of producing exercise-induced anaphylaxis (EIA) and food-dependent exercise-induced anaphylaxis (FDEIA), conditions first described in the 1970s and shown by electron microscopy to involve direct structural degranulation of cutaneous mast cells (Sheffer and Austen 1985). On the other hand, regular moderate-intensity physical activity exerts systemic anti-inflammatory effects, improves autonomic balance, and forms the foundation of POTS rehabilitation programs from which many MCAS patients benefit (Trimble et al. 2024). Reconciling these opposing observations is a central challenge for clinicians advising MCAS patients about safe physical activity.

Research Objective.

This narrative literature review aims to synthesize the current state of knowledge on MCAS pathophysiology, evidence-based strategies for flare-up prevention, and the complex relationship between physical exercise and mast cell activation, with particular attention to clinical implications for sport and rehabilitation medicine.

Research Problems.

What are the established and proposed pathophysiological mechanisms driving MCAS? What pharmacological and non-pharmacological strategies effectively prevent MCAS flare-ups? How does physical exercise interact with mast cell biology, and what exercise modalities can be safely recommended for individuals with MCAS?

Research Hypotheses.

We hypothesize that the available literature supports a graded, individualized exercise approach for MCAS patients, one that accounts for trigger identification, pharmacological premedication, and progressive loading, and that the apparent contradiction between exercise as trigger and exercise as therapy can be resolved through attention to intensity, modality, timing, and cofactor management.

2. Research materials and methods

2.1. Search Strategy and Databases.

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, and Web of Science using the following search terms and Boolean combinations: ("mast cell activation syndrome" OR "MCAS" OR "mast cell activation") AND ("exercise" OR "physical activity" OR "exercise-induced anaphylaxis" OR "sport"); ("mast cell" OR "histamine") AND ("exercise" OR "exertion"); ("MCAS" OR "mastocytosis") AND ("prevention" OR "treatment" OR "flare"). Additionally, the archives of Quality in Sport (https://apcz.umk.pl/QS) and Journal of Education, Health and Sport (https://apcz.umk.pl/JEHS) were searched using keyword queries for exercise immunology, exercise-induced anaphylaxis, Ehlers-Danlos syndrome, and bronchoconstriction. Reference lists of retrieved systematic reviews were hand-searched for additional relevant publications.

2.2. Inclusion and Exclusion Criteria.

Included were peer-reviewed original research articles, systematic reviews, meta-analyses, consensus documents, position statements, clinical guidelines, and narrative reviews published in English between 1985 and 2025. Case reports were included when they provided

mechanistic or clinical insights not available from larger studies. Excluded were conference abstracts without full-text availability, non-peer-reviewed grey literature, and publications in languages other than English without available translations. No restriction was placed on study design given the narrative character of this review.

2.3. Data collection and analysis.

Data extraction focused on three domains: (a) pathophysiological mechanisms of mast cell activation and MCAS diagnostic criteria; (b) pharmacological and non-pharmacological flare-up prevention strategies with their evidence levels; and (c) physiological interactions between exercise and mast cell biology, clinical reports of exercise-induced mast cell events, and exercise prescription recommendations for MCAS populations. Findings were synthesized narratively and organized thematically rather than subjected to formal meta-analytic pooling, consistent with the heterogeneity of available evidence.

2.3.1. AI.

In preparing this work, the authors used Claude (Anthropic) and ChatGPT (OpenAI) for the purpose of additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and assisting in literature search, suggesting phrasing, and improving language clarity. After using these tools, the authors have reviewed and edited the content as needed and accept full responsibility for the scientific content, interpretation of the literature, and the final version of the manuscript.

3. Research results

3.1. Mast Cell Biology and Activation Pathways

Mast cells originate from pluripotent CD34-positive hematopoietic precursors in the bone marrow. Unlike other granulocytes, they leave the marrow in an immature state and complete their differentiation in target tissues under the influence of stem cell factor (SCF) binding to the receptor tyrosine kinase KIT (CD117). Local tissue signals determine the final phenotype: mucosal mast cells predominantly express tryptase alone (MCT), while connective tissue mast cells co-express tryptase and chymase (MCTC) along with carboxypeptidase A3 (Theoharides et al. 2019). Mature mast cells are long-lived, potentially surviving for months, and they reside strategically at interfaces where the body meets the external environment: dermis, lamina propria of the gut, bronchial submucosa, and perivascular and perineural connective tissue.

Activation of mast cells proceeds through multiple pathways. The classical IgE-dependent route involves crosslinking of allergen-specific IgE bound to the high-affinity receptor FcεRI, triggering rapid exocytosis of preformed granular mediators within seconds to minutes. This is the mechanism underlying typical allergic reactions. In MCAS, however, IgE-independent activation pathways predominate in many patients. These include activation through the Mas-related G-protein coupled receptor X2 (MRGPRX2) by neuropeptides such as substance P, vasoactive intestinal peptide, and corticotropin-releasing hormone; complement-mediated activation via C3a and C5a receptors; Toll-like receptor (TLR) signaling, particularly TLR2 and TLR4, by pathogen-associated and damage-associated molecular patterns; and direct pharmacological activation by drugs including opioids, fluoroquinolones, vancomycin, neuromuscular blocking agents, and radiocontrast media (Lide et al. 2022; Valent et al. 2020).

The mediator profile released upon activation falls into three temporal categories. Preformed mediators (histamine, tryptase, chymase, heparin, TNF-α, and proteoglycans) are released within minutes and account for the acute phase of mast cell reactions: vasodilation, increased vascular permeability, smooth muscle contraction, and pruritus. Newly synthesized lipid mediators (prostaglandin D2, leukotrienes LTC4/D4/E4, and platelet-activating factor) appear over 15-30 minutes and sustain bronchoconstriction, mucus secretion, and inflammatory cell recruitment. Finally, de novo cytokine production (IL-1β, IL-6, IL-8, IL-13, IL-31, IL-33, TNF-α, and vascular endothelial growth factor) unfolds over hours and drives the chronic, smoldering inflammatory phenotype that characterizes persistent MCAS (Theoharides et al. 2019; Valent et al. 2020).

3.2. Diagnostic Classification and the Criteria Debate

The current international consensus, led by Valent and colleagues, classifies mast cell activation disorders into four categories. Primary or clonal MCAS is diagnosed when activating symptoms accompany evidence of clonal mast cell disease, typically a somatic gain-of-function KIT D816V mutation or aberrant CD25/CD2 expression on mast cells, even in the absence of full criteria for systemic mastocytosis. Secondary MCAS occurs when a known external trigger, most often IgE-mediated allergy, drives the activation. Idiopathic MCAS applies when recurrent activation episodes meet all three diagnostic pillars (clinical, biochemical, and therapeutic) but no clonal or allergic aetiology can be identified. Mixed forms, combining features of more than one category, are also acknowledged (Valent et al. 2019; Valent et al. 2022).

The three diagnostic pillars of the Valent consensus are: (1) recurrent, episodic symptoms of mast cell mediator release affecting at least two organ systems; (2) documentation of a rise in serum tryptase during or shortly after an event, calculated as a minimum increase of 20% above the individual's baseline plus 2 ng/mL, the so-called "20% + 2" formula; and (3) a meaningful clinical response to medications that target mast cell mediator production or action (Akin et al. 2010; Valent et al. 2019). The tryptase formula was validated prospectively and provides high specificity, though it demands that blood be drawn within a narrow window (ideally 30 minutes to 2 hours) after symptom onset, which is logistically difficult outside hospital settings.

An alternative diagnostic framework, "Consensus-2", proposed by Afrin and Molderings, broadens the biochemical criterion by accepting elevations in urinary mediator metabolites (N-methylhistamine, prostaglandin D2, leukotriene E4, and 11β-prostaglandin F2α) collected over 24 hours during or after a flare (Afrin et al. 2021). Proponents argue that tryptase is an insensitive marker in patients whose mast cells release predominantly non-tryptase mediators. Critics counter that the broader criteria sacrifice specificity, risk overdiagnosis in populations with nonspecific symptoms, and conflate histamine intolerance with true mast cell activation disease (Valent et al. 2022). The clinical consequences of this disagreement are substantial: Yao et al. (2025) demonstrated that among 100 consecutive POTS patients, MCAS prevalence ranged from 2% under Valent criteria to 37% under Consensus-2 criteria, an 18-fold difference driven entirely by definitional choice rather than biology.

A further modifier is hereditary alpha-tryptasemia (HαT), an autosomal-dominant condition caused by germline duplications of the TPSAB1 gene encoding alpha-tryptase. Present in 4-6% of the general population of European descent, HαT produces elevated basal serum tryptase (typically 8-25 ng/mL) and is associated with increased frequency and severity of anaphylaxis, multisystem complaints including gastrointestinal dysmotility, joint hypermobility, and dysautonomia (Lyons et al. 2016; Luskin et al. 2021). HαT can mimic, overlap with, or amplify MCAS, and testing for TPSAB1 copy number should be considered in any patient with persistently elevated basal tryptase above 8 ng/mL.

3.3. The MCAS-POTS-hEDS Overlap

The co-occurrence of MCAS with hypermobile Ehlers-Danlos syndrome (hEDS) and postural orthostatic tachycardia syndrome (POTS) has been reported with increasing frequency in clinical practice, though the mechanistic basis for this clustering remains speculative.

Proposed links include tryptase-mediated degradation of extracellular matrix proteins contributing to tissue laxity, mast cell mediator effects on vascular tone and autonomic reflexes, and shared genetic susceptibility involving connective tissue and mast cell regulatory genes (Kohn and Chang 2020). Mast cells are known to densely populate perivascular and perineural niches, positioning them to influence both vascular reactivity and autonomic signaling.

The practical consequence of this triad for exercise prescription is considerable. POTS limits upright exercise tolerance through excessive heart rate acceleration, orthostatic symptoms, and exercise-induced fatigue. hEDS contributes joint instability, proprioceptive deficits, and injury risk. MCAS adds the possibility of exercise-triggered mediator release with flushing, urticaria, bronchospasm, or frank anaphylaxis. Rehabilitation protocols for this patient population must therefore simultaneously address cardiovascular deconditioning, musculoskeletal vulnerability, and mast cell hyperreactivity, a triple constraint that demands individualization (Stasiak et al. 2025; Trimble et al. 2024).

3.4. Prevention of MCAS Flare-ups: Triggers and Pharmacotherapy

Trigger identification is the foundation of MCAS management. Triggers vary widely between individuals and may include foods (particularly histamine-rich products such as aged cheeses, cured meats, fermented foods, alcohol, tomatoes, and shellfish), environmental exposures (temperature extremes, fragrances, mould, chemical irritants), medications (NSAIDs, opioids, vancomycin, certain antibiotics, radiocontrast media), infections (including SARS-CoV-2), mechanical stimulation (pressure, vibration, friction), emotional stress, hormonal fluctuations across the menstrual cycle, and physical exertion itself (Afrin et al. 2017; Lide et al. 2022). A structured symptom diary correlating exposures with flare episodes is the most effective tool for identifying patient-specific triggers.

Pharmacological prevention follows a stepwise algorithm. First-line therapy consists of daily second-generation H1 antihistamines (cetirizine, fexofenadine, loratadine, or desloratadine) combined with an H2 antihistamine (famotidine 20-40 mg twice daily). Many patients require two to four times the standard antihistamine dose before adequate symptom control is achieved. Second-line additions include oral cromolyn sodium (100-200 mg four times daily before meals), which stabilizes mast cell membranes with minimal systemic absorption and targets gastrointestinal symptoms effectively; ketotifen (1-4 mg daily), a mast cell stabilizer with central H1-blocking properties useful for patients with neuropsychiatric manifestations;

and leukotriene receptor antagonists such as montelukast (10 mg daily), which address respiratory and cutaneous symptoms mediated by cysteinyl leukotrienes (Valent et al. 2019; Molderings et al. 2011).

For patients with prostaglandin-predominant symptoms, particularly flushing, tachycardia, and pain, low-dose aspirin (81-325 mg daily) may provide benefit through cyclooxygenase inhibition, though aspirin tolerance must first be confirmed given that NSAIDs are themselves a common MCAS trigger. In refractory cases, omalizumab (anti-IgE monoclonal antibody, 150-600 mg subcutaneously every 2-4 weeks) has shown efficacy in reducing anaphylactic frequency and severity in both idiopathic anaphylaxis and mast cell-associated anaphylaxis, although large randomized controlled trials specific to strictly defined MCAS are lacking (Giannetti et al. 2020; Brockow et al. 2008).

Non-pharmacological strategies complement medication. The low-histamine diet (restricting aged, fermented, cured, and leftover foods while emphasizing freshly prepared meals) is widely recommended in clinical practice, though it lacks large randomized trials and carries a risk of nutritional inadequacy if maintained indefinitely without dietetic supervision. Diamine oxidase (DAO) enzyme supplementation taken before meals may help patients whose symptoms correlate with dietary histamine load. Quercetin, a natural mast cell stabilizer, has demonstrated in vitro inhibition of histamine and cytokine release from human mast cells exceeding that of cromolyn sodium (Weng et al. 2012). Vitamin C, acting as a cofactor for histamine N-methyltransferase, reduced blood histamine concentrations by 38% in a small but frequently cited clinical study using 2 g daily for two weeks (Johnston et al. 1992). Stress management techniques, including cognitive behavioral therapy, mindfulness meditation, and diaphragmatic breathing, address the neurogenic arm of mast cell activation mediated by corticotropin-releasing hormone and substance P.

3.5. Exercise-Induced Mast Cell Activation

Exercise-induced anaphylaxis (EIA) was first described by Maulitz and colleagues in 1979, and its association with mast cell degranulation was confirmed by Sheffer and Austen (1985), who demonstrated ultrastructural evidence of granule release in skin biopsies obtained from EIA patients immediately after exertion. EIA accounts for an estimated 5-15% of all anaphylactic episodes and occurs predominantly during vigorous aerobic activities such as

running, cycling, and ball sports, though cases have been reported during low-intensity exertion and even brisk walking (Barg et al. 2011; Povesi Dascola and Caffarelli 2012).

Food-dependent exercise-induced anaphylaxis (FDEIA) is a variant in which anaphylaxis occurs only when exercise follows ingestion of a specific food allergen within a 2-6 hour window; neither the food alone nor exercise alone produces symptoms. The most common culprits are wheat (specifically omega-5 gliadin), shellfish, celery, peanuts, and tree nuts. The prevailing mechanistic model implicates exercise-induced increases in gastrointestinal permeability and splanchnic blood flow redistribution, which enhance allergen absorption and systemic presentation to sensitized mast cells in skin and connective tissue (Muñoz-Cano et al. 2017; Szewczyk et al. 2024). Cofactors that lower the activation threshold include concurrent NSAID use, alcohol consumption, sleep deprivation, menstruation, high ambient temperature, and pollen exposure (Feldweg 2015).

Several additional mechanisms have been proposed for exercise-induced mast cell activation beyond the food-dependent pathway. Core body temperature elevation during exercise overlaps with the thermal trigger for cholinergic urticaria, where acetylcholine released at cholinergic synapses activates cutaneous mast cells. Hyperosmolality in contracting muscle and the intestinal lumen may directly lower the threshold for mast cell degranulation. Catecholamine surges alter beta-adrenergic receptor signaling on mast cells. Exercise-associated changes in blood pH and lactate accumulation have been implicated, though direct evidence is limited. Endogenous opioid peptides (beta-endorphins) released during exertion can engage MRGPRX2 receptors. Mechanical stress on perivascular mast cells in connective tissue, especially relevant in hEDS patients with increased tissue laxity, provides yet another plausible trigger (Barg et al. 2011; Černohorská et al. 2025).

A clinically important subgroup of patients labelled with idiopathic EIA harbours occult clonal mast cell disease. The National Institutes of Health conducted a clinical investigation (NCT01326741) to determine the prevalence of clonal mast cell disorders among patients with recurrent unexplained exercise-induced anaphylaxis, finding KIT mutations in a meaningful fraction. This finding highlights the need for systematic bone marrow evaluation and KIT D816V testing in patients with recurrent severe EIA unresponsive to conventional avoidance measures, particularly those with elevated basal serum tryptase.

3.6. Exercise as Therapy: The Anti-Inflammatory Paradox

Despite its potential as a trigger, regular moderate-intensity exercise exerts net anti-inflammatory effects through several well-characterized mechanisms. Contracting skeletal muscle releases interleukin-6 as a myokine, which in turn stimulates production of anti-inflammatory mediators IL-1 receptor antagonist and IL-10 while suppressing TNF-α. Chronic training reduces visceral adiposity and its associated pro-inflammatory cytokine output, improves endothelial function and nitric oxide bioavailability, and enhances vagal tone, all factors that should theoretically reduce mast cell activation over time.

Histamine itself is an integral part of normal exercise physiology. Romero et al. (2017) measured a three-fold increase in skeletal muscle interstitial histamine concentration during 60 minutes of moderate-intensity cycling in healthy adults, attributing this to mast cell degranulation and de novo histamine synthesis within the contracting muscle. This histamine contributes to post-exercise sustained vasodilation and recovery blood flow. Ely et al. (2024) extended this work by showing that combined H1 and H2 receptor blockade during exercise altered the circulating leukocyte and cytokine response, confirming histamine's functional role in the post-exercise inflammatory and reparative cascade. Exercise-associated histamine release is, in other words, a normal physiological process. In MCAS, the pathology lies not in the histamine response itself but in its dysregulation — whether in magnitude, activation threshold, or downstream signaling.

For MCAS patients, and particularly those with the POTS-hEDS-MCAS triad, exercise prescription borrows heavily from the graded exercise training protocols developed for POTS. The Dallas/Levine protocol and the Children's Hospital of Philadelphia (CHOP) programme begin with recumbent or semi-recumbent modalities (recumbent cycling, rowing, swimming) that minimize orthostatic stress while allowing cardiovascular conditioning. Lower-limb and core resistance training (2-3 sessions per week, 10-15 repetitions at moderate load) is incorporated to support venous return and joint stability. Progression to upright modalities proceeds gradually, typically over 8-12 weeks, guided by heart rate targets and the Borg Rating of Perceived Exertion (Trimble et al. 2024). Plizga et al. (2024), reviewing high-intensity interval training outcomes, noted significant cardiovascular and metabolic benefits but also highlighted the risk of adverse events in predisposed populations, a caution directly applicable to MCAS patients, for whom HIIT should be deferred until stable pharmacological control and a robust aerobic base are established.

Practical exercise recommendations for MCAS patients synthesized from the available evidence include the following elements. Pre-exercise pharmacological cover with an H1

antihistamine (cetirizine 10 mg or equivalent) taken 30-60 minutes before exertion, with optional addition of oral cromolyn sodium 200 mg. An adrenaline auto-injector (0.3 mg) must be carried at all times during physical activity. Food-dependent cofactors should be managed by avoiding known or suspected culprit foods for at least 4-6 hours before exercise, and by avoiding alcohol and NSAIDs on exercise days. Sessions should begin with a prolonged warm-up phase (10-15 minutes at low intensity) to allow gradual autonomic adjustment. Recumbent modalities (stationary cycling, rowing, swimming, aquatic exercise) are preferred initially, progressing to upright activities as tolerance permits. Extreme ambient temperatures should be avoided; exercising in a temperature-controlled environment with pre-cooling measures (cold towels, fans) is advisable. A symptom and activity diary should be maintained to identify patterns of post-exertional flares, which may occur with a delay of 4-24 hours. Gentle modalities such as yoga, tai chi, and clinical Pilates serve dual purposes of physical conditioning and autonomic regulation through controlled breathing and parasympathetic engagement (Stasiak et al. 2025).

Table 1. Summary of exercise recommendations for MCAS patients stratified by disease control status.

Phase	Recommended Modalities	Key Precautions
Phase 1: Deconditioned / Unstable MCAS	Recumbent cycling, rowing, aquatic exercise, supine resistance exercises, gentle yoga/stretching	Pre-medicate with H1 antihistamine + cromolyn; carry epinephrine; avoid food 4-6 h pre-exercise; controlled temperature environment
Phase 2: Improving / Stable on Medication	Upright cycling, walking, low-intensity intervals, increased resistance load, Pilates, tai chi	Gradual upright progression; Borg RPE 13-14; monitor for delayed (4-24 h) flares; maintain symptom diary
Phase 3: Well-Controlled MCAS	Jogging, group fitness, moderate HIIT (with caution), sport-specific training	Continue prophylactic antihistamines; avoid known cofactors; exercise with a partner; maintain access to epinephrine

Source: compiled by the authors based on Trimble et al. (2024), Stasiak et al. (2025), and Plizga et al. (2024).

4. Discussion

The central tension in the MCAS literature, and one that this review cannot resolve, is definitional. The choice between the Valent consensus criteria and the Afrin/Molderings Consensus-2 framework determines not only who is diagnosed with MCAS but also how exercise-related mast cell events are interpreted. Under strict criteria, exercise-induced anaphylaxis in a patient without elevated tryptase would not qualify as MCAS; under broad

criteria, it might. This matters for the exercise-and-MCAS intersection because many patients reporting exercise intolerance or post-exertional symptom flares may have mediator profiles that are difficult to capture biochemically, especially outside a research setting. Until prospective studies directly compare mediator kinetics in exercising MCAS patients versus healthy controls, the exercise recommendations in this field will remain rooted primarily in expert opinion, POTS rehabilitation data, and clinical experience.

Several gaps in the literature deserve attention. No randomized controlled trial has yet examined a structured exercise programme in a population defined by strict MCAS criteria. The available exercise evidence is largely derived from POTS studies that include MCAS patients as a subgroup, or from case series and clinical practice guidelines. The physiological work of Romero et al. (2017) and Ely et al. (2024) on exercise-associated histamine dynamics was conducted in healthy volunteers; whether the same mechanisms operate identically, in amplified form, or qualitatively differently in MCAS patients is unknown. Similarly, the efficacy of pre-exercise antihistamine prophylaxis in reducing exercise-triggered mast cell events has not been tested in a controlled setting; it is recommended on pharmacological rationale rather than direct trial evidence.

A broader view from exercise immunology lends theoretical support to the concept of therapeutic exercise in MCAS. Acute bouts of moderate exercise produce transient elevations in skeletal-muscle-derived IL-6, and this myokine response, distinct from the IL-6 elevation seen in chronic inflammation, triggers downstream anti-inflammatory cascades through IL-1 receptor antagonist and IL-10. Whether this pathway operates normally in MCAS patients, whose baseline inflammatory milieu differs from that of healthy controls, has not been directly tested. Animal models of mast cell-driven inflammation suggest that regular moderate exercise reduces tissue mast cell density and mediator content over several weeks, but confirmatory human data in MCAS are absent. Bridging this gap between exercise physiology in healthy volunteers and clinical exercise prescription for MCAS patients represents perhaps the single largest translational need in this area.

The dietary dimension of MCAS management intersects with exercise physiology in important ways. Patients following restrictive low-histamine diets may face caloric and macronutrient shortfalls that impair exercise capacity and recovery. DAO supplementation before meals offers a potential bridge, but its efficacy in the exercise context is untested. Quercetin, despite promising in vitro data, lacks robust clinical trials at doses and durations relevant to mast cell stabilization in exercising individuals. The interaction between gut

permeability changes during exercise and dietary histamine load is a particularly fertile area for future investigation, given its relevance to both FDEIA and broader MCAS flare-up prevention.

From a sport-medicine perspective, the diagnostic overlap between exercise-induced urticaria, cholinergic urticaria, EIA, FDEIA, and MCAS creates confusion for practitioners. Černohorská et al. (2025) highlighted similar diagnostic complexity in exercise-induced bronchoconstriction, where mast cell mediator release in the airways overlaps with but is distinct from classical asthma, a parallel that extends to the systemic mast cell activation seen in MCAS. Clinicians evaluating athletes with unexplained exercise-associated symptoms should consider screening for basal tryptase elevation, TPSAB1 copy number, and, in cases of recurrent severe anaphylaxis, bone marrow evaluation for clonal mast cell disease.

The hEDS-POTS-MCAS triad poses particular rehabilitation challenges. Joint instability limits exercise selection; orthostatic intolerance constrains posture; and mast cell reactivity constrains intensity and environment. The staged approach outlined in Table 1, adapted from the Levine/CHOP POTS protocols and enriched with mast-cell-specific precautions, represents the current best practice synthesis. Stasiak et al. (2025), reviewing rehabilitation outcomes in Ehlers-Danlos syndrome, found that individualized, low-load, proprioception-focused programs improved both function and quality of life, outcomes that are likely transferable to MCAS-hEDS patients, though direct evidence is needed.

From a clinical standpoint, exercise prescription in MCAS cannot follow a one-size-fits-all model. The heterogeneity of triggers, the unpredictability of flare timing, and the frequent comorbidity with POTS and hEDS demand that each programme be developed collaboratively between the treating allergist, a physiotherapist experienced in autonomic dysfunction, and the patient. Pre-exercise pharmacological prophylaxis should be viewed not as optional but as an integral part of the session - analogous to bronchodilator use before exercise in asthma. Delayed post-exertional flares, occurring 4 to 24 hours after activity, are particularly insidious: they may not be recognized as exercise-related, leading to unnecessary activity restriction or diagnostic confusion. Structured symptom diaries that track both immediate and next-day responses are indispensable tools for titrating exercise load in this population.

5. Conclusions

Mast Cell Activation Syndrome represents a clinically heterogeneous condition whose recognition and management continue to evolve. The pathophysiology centers on inappropriate mast cell mediator release through IgE-dependent and, more commonly in MCAS, IgE-independent pathways, producing episodic multisystem symptoms. Diagnostic consensus remains fractured between the strict Valent criteria and the broader Consensus-2 framework, with direct consequences for prevalence estimation and clinical decision-making.

Flare-up prevention rests on three pillars: systematic identification of patient-specific triggers, stepwise pharmacotherapy anchored by H1/H2 antihistamines and expanded with mast cell stabilizers and omalizumab as needed, and supportive non-pharmacological measures including dietary modification, nutraceutical supplementation, and stress management.

Physical exercise occupies a dual role in MCAS. It is a recognized trigger for mast cell degranulation - through thermal, osmolar, mechanical, neuroendocrine, and cofactor-dependent mechanisms - capable of producing exercise-induced anaphylaxis and its food-dependent variant. Simultaneously, regular moderate-intensity exercise exerts anti-inflammatory, autonomic-regulatory, and cardioprotective effects that benefit MCAS patients, particularly those with comorbid POTS and hEDS. The resolution of this paradox lies in individualized exercise prescription: recumbent-biased graded programs, pharmacological premedication, cofactor management, and careful intensity progression guided by symptom monitoring.

Future research should prioritize randomized controlled trials of structured exercise interventions in MCAS-defined populations, biomarker time-course studies comparing mediator kinetics during exercise in MCAS patients versus controls, and evaluation of pre-exercise pharmacological prophylaxis strategies. The Quality in Sport readership is well positioned to contribute to this evidence base, given the journal's focus on the intersection of physical activity, health, and quality of life.

Disclosure

Supplementary Materials

No supplementary materials are associated with this article.

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Conflicts of Interest

The authors declare no conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process

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