Concept Paper

Laxity Comes with Consequences: Connective Tissue Disorders and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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Abstract

ME/CFS patients suffer from manifestations of disturbed connective tissue including ligament laxity, hypermobility, craniocervical instability, and orthostatic intolerance due to connective tissue weakness of large vessels, while muscular capillaries show basement membrane thickening. Mast cell overactivity may destabilize connective tissue through chymase and tryptase, activating collagen-degrading metalloproteinases, while cytokines enhance expression. Hypoxia and ROS-mediated inhibition of prolyl hydroxylases impairs crosslinking of newly formed collagen and reduces hypoxia-inducible factor (HIF)-1α degradation. Chronic HIF-1α elevation, in turn, can worsen connective tissue stability by unfavorably altering its composition as recently shown in tendinopathies. ME/CFS associated skeletal muscle dysfunction affecting neck muscles cannot compensate for ligament laxity to stabilize cervical spine but aggravates instability. In skeletal muscle capillaries, elevated HIF-1α may promote extracellular matrix overproduction and basement membrane thickening, impairing capillary perfusion and diffusion, and glycolytic metabolism. The sensitivity of HIF-2α to ROS-mediated degradation may impair angiogenic maturation; the imbalance between HIF-2 α and HIF-1α may permit sustained HIF-1α–driven extracellular matrix production and reduce capillary density. Overall, there seems to be a bidirectional relationship between connective tissue disorders and ME/CFS, whereby connective tissue disorders may predispose individuals to ME/CFS, and ME/CFS, in turn, may exacerbate the underlying connective tissue pathology.

Keywords: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS); Long COVID; ME/CFS; connective tissue disorders; craniocervical instability; ligament laxity; basement membrane thickening; HIF-1α; reactive oxygen species (ROS); orthostatic intolerance; mast cell hyperactivity

1. Introduction:

Among a variety of symptoms, many ME/CFS patients suffer from manifestations and symptoms of disturbed connective tissue. Marfan-syndrome and hypermobile Ehlers-Danlos-Syndrome (hEDS) are well established co-morbidities or risk factors for ME/CFS (van Dijk et al., 2008), (Roma et al., 2018), (Rowe et al., 1999), (Hakim et al., 2017). Compared with the healthy volunteers significantly more patients with ME/CFS fulfilled the criteria for generalized joint hypermobility (Nijs et al., 2006), (Bragée et al., 2020). Joint hypermobility was found more common in children with chronic fatigue syndrome than in healthy controls (Barron et al., 2002). Both generalized joint hypermobility and extreme hypermobility were reported to be significant risk factors for long COVID or associated with it (Ganesh & Munipalli, 2024), (Torok et al., 2025). Patients show cervical instability, hypermobile joints, stretchy skin, and orthostatic intolerance (van Dijk et al., 2008), (Roma et al., 2018), (Rowe et al., 1999), (Hakim et al., 2017), (Rowe et al., 2017), (van Campen et al., 2020), (Ganesh & Munipalli, 2024).

ME/CFS with concurrent joint hypermobility and EDS was associated with more severe symptoms and greater functional impairment (Mudie et al., 2024). In that study, 15.5% of ME/CFS

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patients were classified as having joint hypermobility. Other studies have reported prevalences of joint hypermobility approaching 20% (Nijs et al., 2006), (van Campen et al., 2021). Notably, van Campen et al. found that hypermobile patients exhibited significantly higher rates of postural orthostatic tachycardia syndrome (POTS) during tilt-table testing compared to non-hypermobile patients. In contrast, Bragée et al. ((Bragée et al., 2020) reported a substantially higher prevalence of approximately 50%.

The aim of this paper is to provide explanations for the disturbances of connective tissue and collagen in ME/CFS and to explain the relationship between both. Orthostatic intolerance must be included in these considerations because the weakness of the connective tissue of capacitance blood vessels, of veins and large arteries, impairs cardiovascular regulation for proper orthostatic function and for cardiovascular adaptation to exercise (rise in cardiac preload necessary for raising cardiac output). Basement membrane thickening has been found in skeletal muscle capillaries in biopsies of ME/CFS patients (Hejbøl et al., 2022), (Aschman et al., 2023), (Charlton et al., 2025), (Slaghekke et al., 2025). The most important component of the extracellular matrix of capillary basement membrane is collagen (mainly type 4) (Alberts, 2022).

In the first part of this paper I explain how ME/CFS could impair the quality and stability of connective tissue of ligaments and blood vessels (to cause orthostatic dysfunction) and how ligament laxity interacts with the skeletal muscle pathology of ME/CFS to cause craniocervical instability.

In the second part, I examine potential mechanisms driving capillary basement membrane thickening and extracellular matrix accumulation, situating these changes within the broader framework of dysregulated angiogenesis and related processes that may contribute to the chronification of ME/CFS. This perspective extends beyond connective tissue abnormalities to address the question why spontaneous recovery is so rare in ME/CFS.

2. Major Manifestations of Connective Tissue Disturbances in ME/CFS

2.1. Orthostatic Intolerance

An important cause of orthostatic intolerance is disturbed connective tissue of blood vessels, particularly the capacitance vessels, veins and large arteries. Veins can be overstretched by the distending effect of the blood following gravitation when standing up. This decreases the circulating blood volume to diminish cardiac filling, preload and cardiac stroke volume and cerebral blood flow (Joseph et al., 2021). Patients with hypermobility show orthostatic intolerance, fatigue and autonomic dysfunction (Stewart, 2013), (De Wandele et al., 2016), (Celletti et al., 2017), (Roma et al., 2018), (Peebles et al., 2022). ME/CFS patients with joint hypermobility showed larger cerebral blood flow reductions during orthostatic stress testing than patients without hypermobility (van Campen et al., 2021). The decrease in cerebral blood flow finally accounts for the symptoms and the orthostatic stress (van Campen et al., 2023). Orthostatic stress can be considered a risk factor for ME/CFS. The main mechanism could be desensitization of ß2-adrenergic receptors which are most important for performing muscle work (Wirth & Scheibenbogen, 2020).

Wall tension increases proportional to the radius of the distended vessel according to Laplace's law and so does the force needed to contract the (distended) vessel for raising cardiac filling and preload and circulating blood volume. Thus, excessive distension due to disturbed vascular connective tissue does not only impair the ability of actively correcting for the gravity induced venous distension and ensuing loss of cardiac preload, but it also reduces the ability to raise cardiac output for performing exercise in the upright position (exercise capacity). If connective tissue interposed between smooth muscle cells is also lax, contractions could also become inefficient.

During exercise cardiac output can rise by a factor of 4-6 for which the contraction of capacitance vessels and the ensuing higher cardiac filling is a prerequisite (cardiac preload). This means that a loss of circulating blood volume by distended capacitance vessels lowers cardiac preload, stroke volume and brain perfusion giving rise to symptoms and orthostatic stress.

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2.2. Laxity of Ligaments and Craniocervical Instability

Patients also report on hypermobility and stretchy skin that have developed since the disease onset or have become apparent afterwards. Many patients seem to have preexisting, at least mild hypermobility themselves or in their families, pointing to an inherited predisposition although there is no firm database to show this. A reasonable assumption is that some degree of connective tissue disorder is present in many patients before disease onset as a latent or minor disorder and becomes apparent or aggravated by ME/CFS. How could ME/CFS via ME/CFS related pathomechanisms worsen the quality and stability of the connective tissue? These pathomechanisms will be addressed below in length.

Craniocervical instability is frequent in ME/CFS patients (Bragée et al., 2020), (Frost & Barclay, 2024). It is particularly disturbing and causes a wide range of symptoms via compression or irritation of adjacent structures such as brain stem, vagal nerve, and sympathetic trunk to disturb autonomic function, nerves and blood vessels. Compression of veins may diminish venous flow and by that perfusion. How cervicocranial instability can exert deformative force on the brain stem to disturb centers involved in autonomic regulation is described in a recent publication (Wood et al., 2025). Spinal disorders such as Chiari malformation and craniocervical instability can impair the drainage of cerebrospinal fluid, resulting in an increase in intracranial pressure that can lead to brainstem compression and disturb autonomic function (Bragée et al., 2020), (Henderson Sr et al., 2024).

Bone, cartilage, intervertebral discs, joints, ligaments and skeletal muscle together finally account for the stability and motility of the vertebral column. Lax ligaments are reasonably implicated as the cause of cervical instability (Frost & Barclay, 2024), (Bragée et al., 2020), but there may be a skeletal muscle factor in ME/CFS that contributes. The latter manifests as loss of force and endurance due to malperfusion, diffusion disturbances, mitochondrial dysfunction and skeletal muscle damage (Appelman et al., 2024), (Joseph et al., 2021), (Paffrath et al., 2024), (Jäkel et al., 2021), (Nacul et al., 2018), (do Amaral et al., 2024), (Jothi et al., 2025), (Bizjak et al., 2024). Neck and throat muscles are affected by the skeletal muscle pathophysiology of ME/CFS and may be involved in craniocervical instability. Interestingly, in a PET-CT study with a tracer for the mitochondrial protein TSPO the neck and throat muscles were lighting up and were among the most strongly affected muscles in the body of ME/CFS patients in this study (James, M., 2025). With the development of ME/CFS and skeletal muscle pathology, these muscles can become dysfunctional and fail as a compensatory mechanism to improve cervical stability or even contribute to craniocervical instability. One of the rehabilitation treatments in craniocervical instability is targeted strengthening of deep neck flexors, extensors, and postural muscles that can greatly improve stability in otherwise healthy subjects (Russek et al., 2023). Since muscle function is disturbed and exercise can worsen complaints and cause PEM, it is not surprising that craniocervical instability does not improve and, attempts to strengthen neck muscle in ME/CFS patients with craniocervical instability can fail. Skeletal muscle dysfunction of throat and neck muscles even seems to be a destabilizing factor on its own in the development of craniocervial instability.

ME/CFS also develops after physical trauma, particularly after car accidents with whiplash injuries, pointing to the trauma as the trigger. According to the assumptions made above it is reasonable to postulate that subjects with a preexisting ligament laxity, which may only be latent at the time of the trauma, are particularly affected by such trauma, but data are missing from the literature.

A theoretical possibility is that many patients affected have a genetic predisposition for connective tissue diseases. Due to a concomitant weakness of vascular connective tissue of the large blood vessels these subjects are likely to also have a predisposition for ME/CFS via a propensity for orthostatic intolerance. In accordance with this postulate, patients with hEDS were more likely to be diagnosed with Long COVID compared to similar patients without hEDS. hEDS patients face higher risks after COVID-19 (Pearson et al., 2025).

Stress after the accidents and residual complaints may favor the development of ME/CFS together with autonomic dysfunction. Autonomic dysfunction, which plays an important role in the

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pathogenesis of ME/CFS, can even be caused or increased by craniocervical instability via irritation of contiguous structures, the sympathetic cervical trunk, the glomus caroticum, the vagal nerve, compression of the vertebral artery, proprioceptive dysfunction and compression of the lower brainstem. The clinical picture can be confusing. Craniocervical instability has also been reported to co-occur with tethered cord syndrome (Gensemer et al., 2024). It has been hypothesized that increased motion at the skull–neck junction may transmit mechanical forces along the spinal cord, potentially increasing strain in the tethered cord and leading to neural irritation (Klinge et al., 2021).

3. Potential Mechanisms of Deterioration of the Quality of Connective Tissue in ME/CFS

3.1. Enhanced Degradation of Connective Tissue by Mast Cells and Inflammation

Among a variety of substances mast cells synthesize, store, and release the serine proteases tryptase and chymase from cytoplasmic secretory granules (Schwartz, 1990), (Wernersson & Pejler, 2014), (Krystel-Whittemore et al., 2016). These enzymes can activate matrix metalloproteinases (MMPs) that degrade collagen (Gruber et al., 1989), (Lees et al., 1994), (Caughey, 2011), (Monaco et al., 2022). Turnover of connective tissue is very low, but degradation should be accelerated by MMPs activated by tryptase and chymase released from mast cells. Mast cell hypersensitivity and hEDS were found associated (Monaco et al., 2022), (Shirvani et al., 2024). Mast cell overactivity is also frequently associated with ME/CFS. Approximately one-quarter of ME/CFS patients demonstrate clinically relevant mast cell activation, often involving multiple organ systems and responding to mast-cell–targeted therapy (Rohrhofer et al., 2025).

Multiple proinflammatory cytokines such as IL-1β and TNF-α are elevated in ME/CFS and correlate with malaise and autonomic symptoms, though findings can vary (Montoya et al., 2017), (Giloteaux et al., 2023). Cytokines (IL-1β, TNF-α) upregulate MMPs (Kinne et al., 2002), (Y. Zhang et al., 2017).

Cerebrospinal fluid immune phenotyping identified two distinct immunotypes in ME/CFS patients (Bastos et al., 2025). One subgroup, characterized by elevated levels of MMP-1, MMP-2, and MMP-10, also showed increased cytokine concentrations. However, this immunotype was not associated with a higher prevalence of POTS or increased joint hypermobility. Moreover, no significant differences in total plasma levels of these markers were observed between ME/CFS patients and control subjects. These findings suggest an association between MMP activity and cytokine signaling within the central nervous system. At the same time, the absence of elevated plasma MMP levels indicates that systemic increases are unlikely, although modest, localized elevations in connective tissue cannot be excluded.

Altogether, mast cell overactivity and low-grade inflammation may contribute to destabilization of connective tissue in ME/CFS. As will be discussed in detail below, the newly synthesized collagen that replaces degraded connective tissue could be of lower quality.

3.2. Decreased Stability of Newly Formed Connective Tissue

3.2.1. The Potential Pathophysiological Role of Prolyl Hydroxylase Inhibition for the Impairment of the Stability of Collagen

In the following I try to explain how the quality of newly formed connective tissue and ligaments could be impaired by pathomechanisms involved in ME/CFS. An important enzyme in the formation of collagen are prolyl hydroxylases (PHDs) which hydroxylate prolin to hydroxyproline (Gorres & Raines, 2010), (Rappu et al., 2019), (Fong & Takeda, 2008). There are three isoforms of collagen-stabilizing PHDs and three isoforms of hypoxia-inducible factor (HIF)-inactivating PHDs (Myllyharju, 2008). Lysyl-hydroxylases are also involved in crosslinking collagen and are also hypoxia-sensitive. Thereafter, lysyl-oxidase (LOX) catalyzes the oxidative deamination of lysine and hydroxylysine residues in collagen and elastin, enabling crosslinking of the extracellular matrix (ECM). This crosslinking is essential for tissue strength and stiffness. These enzymes tighten the

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collagen bundles via formation of hydrogen bonds as the final step in the synthesis of collagen. Importantly, PHDs and lysyl-hydroxylases are inhibited by both hypoxia and reactive oxygen species (ROS). ROS oxidizes the catalytic center, Fe^{2+} to Fe^{3+}, inactivating the enzyme (Lee et al., 2016), (Fong & Takeda, 2008). Inhibition of PHDs in hypoxia or by ROS worsens stability of collagen and allows HIF-levels to rise and to exert their physiological functions. Mitochondrial dysfunction is present in skeletal muscle in ME/CFS and produces ROS (Paul et al., 2021), (Jammes et al., 2020), (Bizjak et al., 2024). Consequently, the final steps of collagen formation may not proceed properly, leading to connective tissue weakness. The relative contributions of hypoxia and ROS to PHD inhibition are discussed below.

3.2.2. The Potential Role of HIF-1α in Deteriorating the Quality of Connective Tissue

PHDs have an important enzymatic function beyond their role in collagen maturation: They act as oxygen sensors. Under normoxic conditions, PHDs hydroxylate hypoxia-inducible factor-1α (HIF-1α) and hypoxia-inducible factor-2α (HIF-2α), marking them for rapid proteasomal degradation and thus inactivation. During hypoxia, this inactivation by PHD is absent, allowing HIF-1α and HIF-2α to accumulate and initiate adaptive responses (Kumar & Choi, 2015), (Albanese et al., 2020), (Kierans & Taylor, 2021). With regard to HIF-1α, these include stimulation of glycolysis, reduction of mitochondrial mass, and promotion of extracellular matrix (ECM) synthesis during angiogenesis (Guarnieri et al., 2024) (Table 1).

Table 1. Biological effects of HIF-1α compared with HIF-2α and biopsy findings in skeletal muscle in ME/CFS.

Biological effect	**HIF-1α**	**HIF-2α**	**Findings in ME/CFS**
Adaptation to hypoxia	acute	chronic	n.a.
Main HIF-inactivating PHD isoenzyme	PHD2	PHD3	n.a.
Sensitivity of HIF to degradation by calpain via bursts of ROS	no	yes	n.a.
Stimulation of glycolysis	↑	-	↑
Fast twitch muscle fibers	↑	(↓)	↑
Mitochondrial biomass	↓	(↑)	↓
Slow oxidative muscle fiber	↓	(↑)	↓
Stimulation of angiogenesis	initiation	maturation	capillary density reduced
Stimulation of extracellular matrix formation of basement membranes	↑	-	↑

HIF-1α is an intracellular transcription factor, not a secreted ligand, an important distinction to consider when attempting to measure its levels. The role of HIF-2α is explained below.
Increased glycolytic fibers, reduced mitochondrial biomass PASC (Appelman et al., 2024), (Colosio et al., 2023) and excessive ECM accumulation seen as basement membrane thickening and amyloid deposits have been observed in skeletal muscle of ME/CFS or PASC patients (Aschman et al., 2023), (Hejbøl et al., 2022), (Charlton et al., 2025), (Slaghekke et al., 2025). These findings are fully consistent with HIF-1α activity, although direct evidence for increased HIF-1α levels in ME/CFS muscle tissue is still lacking.

A recent publication reveals that HIF-1α is a major driver of tendinopathies (Moschini et al., 2025). HIF-1α upregulates profibrotic mediators such as CTGF, TIMP-1, and PAI-1 ((Higgins et al., 2004), (Kietzmann et al., 1999). Its demonstrated overactivity clearly worsens the quality of the tendon tissue in these investigations (Moschini et al., 2025). Its release in tendons after stretch is independent of hypoxia or ROS but caused by a stretch sensitive mechanism that leads to a calcium-mediated

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production of HIF-1α. Chronic HIF-1α in tendons exposed to mechanical overload causes overstimulation and disorganization of the tendinous connective tissue, mainly by changing the composition of the collagen types (less of the typical collagen type 1) and increased cross-linking (Moschini et al., 2025). There is no hypoxia and no obvious reasons for high ROS in tendinopathies that could inhibit prolyl- and lysyl-hydroxylases. Despite higher cross-linking, the mechanical properties of the tendons worsened in these investigations in tendons due to disorganization of the tissue and altered composition. What can be concluded from the role of HIF-1α in tendinopathies with respect to ME/CFS is that chronically elevated HIF-1α alone could considerably worsen the properties of connective tissue.

In contrast to tendinopathies, ME/CFS is associated with hypoxia and increased ROS, both of which can elevate HIF-1α levels. However, it should also be considered that, in addition to hypoxia and ROS, excessive distension of weakened connective tissue may further raise HIF-1α levels in ME/CFS if the stretch-sensitive, calcium-mediated mechanism described in tendons also operates in ligaments. Because ligament stability is impaired in ME/CFS, these tissues may be more easily distended, thereby activating this potential stretch-sensitive mechanism promoting HIF-1α release. HIF-1α would not be rapidly degraded by PHDs, as their activity is inhibited by hypoxia or ROS. Consequently, local HIF-1α levels could rise markedly through the synergistic effects of excessive mechanical stretch in lax ligaments potentially promoting HIF-1α production and impaired degradation of HIF-1α due to hypoxia or ROS, potentially leading to unfavorable alterations in ligament composition similar to those described in tendinopathies.

Due to its importance for the stabilization of collagen and connective tissue and its inhibition by ROS and inactivation of HIF, disturbed or inhibited PHD activity thus becomes a potential pathomechanism causing the connective tissue disorders that develop with ME/CFS by two mechanisms:1) the crosslinking effect of PHD is impaired. 2) HIF-1α rises because it is not continuously degraded by PHD to have its own deteriorating effect on the mechanical properties of connective tissue as shown in tendinopathies. HIF-1α may also rise due to overdistension of weakened connective tissue by a stretch-sensitive mechanisms of HIF-1α release as assumed for tendinopathies.

A proposed explanation for the association between connective tissue disorders and ME/CFS is that acquired craniocervical instability exerts deformative forces on the brainstem, where key centers of autonomic regulation are located. According to Wood et al. (Wood et al., 2025) “the proposed causal chain begins with a trigger, such as an infection, that leads to connective tissue compromise, which in turn causes brainstem deformative stress, ultimately resulting in multisystem dysfunction with secondary effects.” This hypothesis suggests that an acquired connective tissue disorder may lead to autonomic dysfunction, thereby contributing to the development of ME/CFS. Importantly, this does not contradict the hypothesis outlined here. While ME/CFS through mechanisms involving ROS and HIF-1α may impair connective tissue integrity, factors such as hypoxia (raising HIF-1α), mast cell hyperactivity, and pro-inflammatory cytokines, which can increase MMP expression, can already be present following the acute COVID-19 infection. Consequently, connective tissue degradation may begin early in the disease course with the acute infection and persist or even intensify following the development of ME/CFS.

In summary, connective tissue disorders or worsening of existing conditions may arise from increased tissue degradation and impaired connective tissue formation and repair. Enhanced degradation may result from upregulated matrix MMPs, stimulated by mast cell–derived enzymes or cytokines, while new formation and repair may be impaired by disturbed PHD activity and the resulting altered HIF-1α signaling, leading to reduced collagen stability. Impaired collagen stability may affect not only ligaments and skin, but also the connective tissue of capacitance blood vessels. This may represent a pathomechanism through which orthostatic dysfunction is caused, exacerbated and sustained to contribute to the chronification of ME/CFS.

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4. Pre-Existing Connective Tissue Disorders as a Risk Factor for ME/CFS and Worsening After Disease Onset

Individuals with pre-existing or latent connective tissue disorders may be particularly susceptible to the disturbances in connective tissue degradation and regeneration acquired with the development of ME/CFS just described. In this context, connective tissue disorders may rapidly worsen or become clinically apparent following the onset of ME/CFS and, in turn, contribute to worsening and chronification of ME/CFS.

ME/CFS with concurrent joint hypermobility and EDS was associated with more severe symptoms and greater functional impairment (Mudie et al., 2024). This subgroup of ME/CFS patients with hypermobility with more females, EDS, POTS was also significantly more likely to report a family history of EDS.

Pre-existing connective tissue disorders may constitute a risk factor for ME/CFS by predisposing affected individuals to orthostatic intolerance and related physiological stress due to disturbed vascular connective tissue, as well as to craniocervical instability accompanied by pain and irritation of adjacent tissues, which may impair autonomic function (Wood et al., 2025). Autonomic dysfunction, in turn, is centrally involved in the pathophysiology of ME/CFS. Notably, orthostatic dysfunction represents a major risk factor for ME/CFS, as sustained orthostatic stress and tissue malperfusion can promote disease development (Wirth & Scheibenbogen, 2020).

Furthermore, pre-existing connective tissue disorders, including latent forms, may even increase vulnerability to trauma leading to craniocervical instability, which, in turn, may facilitate the development or progression of ME/CFS as just outlined. Thus, connective tissue disorders, even latent ones, may predispose to ME/CFS, and ME/CFS, in turn, may aggravate the connective tissue disorder.

5. hEDS: More than a Connective Tissue Disorder?

HEDS may not only affect connective tissue. Mast cell overactivity has been reported in hEDS and may contribute to the deterioration of connective tissue, as mentioned above (Shirvani et al., 2024). A relationship between hEDS, POTS, and mast cell activation syndrome was also reported by other authors (Kucharik & Chang, 2020), (Ganesh & Munipalli, 2024). Key findings in Long COVID and ME/CFS, including cerebrovascular, respiratory, and cardiovascular dysregulation, as well as neurodegeneration (e.g., small fiber neuropathy and mast cell hyperactivity) were not exclusive to these syndromes; comparable abnormalities, albeit with differing patterns and distributions, were also observed in hEDS when the three conditions were compared (Novak et al., 2026).

While orthopedic complaints associated with hypermobility and orthostatic intolerance resulting from impaired vascular connective tissue can be readily understood as consequences of connective tissue weakness, the link between hypermobility (in patients without a diagnosis of ME/CFS) and small fiber neuropathy, mast cell hyperactivity and dysautonomia remains less understood or even unexplained. It is uncertain whether these features represent primary disturbances or arise secondarily over time as a consequence of the underlying connective tissue disorder through mechanisms that are not yet understood. Notably, these abnormalities associated with hypermobility are also commonly observed in ME/CFS and can be considered potential risk factors.

Primary mast cell overactivity may indirectly promote collagen degradation through the release of tryptase and chymase, which activate matrix metalloproteinases (MMPs), as noted above. Notably, mast cell overactivity itself has been associated with small fiber neuropathy (Novak et al., 2022). The potential mechanisms by which mast cell overactivity could contribute to small fiber neuropathy in Long COVID are discussed in a recent publication (Morcos & Theoharides, 2026).

Conversely, the mechanisms by which primary hEDS may induce mast cell overactivity remain poorly understood. One potential pathway for consideration involves HIF-1α. HIF-1α is produced by the mast cell itself and has been shown to enhance mast cell effector functions (Walczak-

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Drzewiecka et al., 2008), (Branitzki-Heinemann et al., 2012), suggesting it may play a role in linking connective tissue abnormalities to dysregulated mast cell behavior. Interestingly, mast cells are also present in skeletal muscle (Van der Stede et al., 2025) where hypoxia is present and ROS is produced during exercise in Long COVID or ME/CFS to increase HIF-1α in local mast cells to raise their responsiveness and activity. By the way, this is an interesting pathomechanism to consider in the exercise related skeletal muscle pathophysiology and PEM in ME/CFS. Since HIF-1α is generally assumed to be upregulated in response to hypoxia or ROS, it is necessary to explicitly explain how this mechanism could operate in hEDS prior to triggers such as infection, impaired perfusion or the onset of mitochondrial dysfunction producing ROS. Accordingly, while HIF-1α may contribute to or exacerbate mast cell activity in Long COVID or ME/CFS, there is no obvious cause for an early or primary co-occurrence of hEDS with mast cell overactivity involving HIF-1α.

Orthostatic intolerance, including postural orthostatic tachycardia syndrome (POTS), may be partly explained by structural weakness of the large capacitance vessels in hEDS. Concomitant mast cell hyperactivity could further exacerbate this problem, producing a synergistic impairment of vascular and orthostatic regulation. Histamine's vascular effects such as venous dilation, redistribution of arterial blood flow (a "steal" effect in histamine-rich vascular beds like the intestine) and increased microvascular permeability leading to plasma leakage and hypovolemia are likely involved in this mechanism (Wirth & Löhn, 2023), (Wirth & Löhn, 2024).

The co-occurrence of connective tissue disorders affecting vascular tissue and elevated histamine activity may therefore contribute to both orthostatic and exercise intolerance. This may occur through an impaired ability to sufficiently increase cardiac output (i.e., preload failure) and to appropriately direct perfusion toward skeletal muscle during exercise, partly due to arterial steal phenomena in histamine-rich tissues. The resulting orthostatic stress may, in turn, promote desensitization of β2-adrenergic receptors (ß2AdR) which play a key role in increasing cerebral, cardiac, and skeletal muscle blood flow during exercise, as well as in stimulating Na^+/K^+-ATPase activity in skeletal muscle (Clausen, 2003), (Pirkmajer & Chibalin, 2016). In addition, calcitonin gene-related peptide (CGRP), which is released from small sensory nerve fibers to stimulate perfusion and particularly to activate the Na^+/K^+-ATPase activity during exercise together with ß2AdR must be reduced in the presence of small fiber neuropathy. The resulting rise in intracellular sodium due to deficient Na^+/K^+-ATPase activity can cause a rise in mitochondrial calcium resulting in calcium overload and mitochondrial dysfunction and damage (Wirth & Scheibenbogen, 2021), (Scheibenbogen & Wirth, 2025). Given that small fiber neuropathy appears to be relatively prevalent in hEDS, this disturbance could further compromise vascular and metabolic function.

Taken together, the combination of hEDS, mast cell hyperactivity, small fiber neuropathy and orthostatic intolerance may represent a significant cluster of risk factors for ME/CFS. This raises the possibility that these conditions lie along a pathophysiological continuum, extending from joint hypermobility to ME/CFS. In the presence of such concomitant disorders and risk factors, patients may be particularly vulnerable to the development of ME/CFS. A trigger such as an infection could ultimately precipitate ME/CFS as the final step in this disease process, potentially via the development of mitochondrial disturbance in skeletal muscle, from which recovery is hardly possible because the disturbance is sufficiently self-sustaining. These considerations suggest that consistent, early management of these associated comorbidities of hEDS may be crucial in preventing progression to ME/CFS.

A recent study reported immune dysregulation involving the complement system and profibrotic cytokines as a key feature of hEDS. According to the authors, this challenges the view of hEDS as only a connective tissue disorder, supporting a broader model that includes innate immune dysfunction (Griggs et al., 2025). Another interesting findings in this context is that variants in genes associated with mitochondrial function and immune regulation were found enriched in hEDS, suggesting a potential link to the mitochondrial dysfunction and autoimmune mechanisms also implicated in the pathogenesis of ME/CFS (Shirvani et al., 2025). It remains to be elucidated whether

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and how immunological disturbances and mitochondrial gene variants reported in these publications may contribute to the development or progression of ME/CFS.

Disturbances in mitochondrial function including stimulation of glycolysis have also been linked with Marfan syndrome and other genetic variants in the context of aortic aneurysms (Marcos-Ríos et al., 2025). In congenital connective tissue disorders, relatively mild inherited mitochondrial abnormalities may be present that could predispose individuals to ME/CFS-specific pathomechanisms, which ultimately lead to the pronounced mitochondrial dysfunction observed in the disease in this context (Scheibenbogen & Wirth, 2025). Inherited mitochondrial and immunological alterations may thus constitute additional risk factors for the development of ME/CFS, beyond the contribution of altered vascular connective tissue in capacitance vessels and the (autonomic) disturbances associated with craniocervical instability.

6. Hypoxia Versus Pseudohypoxia as the Mechanism of Inhibition of PHDs

Activation of hypoxic signaling does not require true hypoxia. In ME/CFS, which may develop as the most serious sequel, ROS produced through mitochondrial dysfunction could be the main factor inhibiting PHD. ROS and many other stress signals can also induce HIF accumulation even at normoxia, so called pseudohypoxia (Salminen et al., 2016). Accordingly, pseudohypoxia occurs when ROS oxidize the catalytic Fe^{2+} center of PHDs, inhibiting the enzyme and preventing HIF degradation. Given the evidence of elevated ROS production in ME/CFS (Jammes et al., 2020), ROS-mediated PHD inhibition in skeletal muscle can be reasonably assumed. The role of oxygen and hypoxia in activating HIF in skeletal muscle in ME/CFS is not clear for the following reasons: Venous O_2 partial pressure is paradoxically elevated (Joseph et al., 2021), (Jothi et al., 2025). Mitochondrial dysfunction, disturbed diffusion and glycolytic metabolism reduce oxygen utilization. The observation of arteriovenous shunting may also raise venous oxygen partial pressure despite reduced perfusion (Joseph et al., 2021). True hypoxia could be caused by a lower cardiac output during exercise and impairment of capillary flow by decreased capillary density, lumen narrowing by thickened basement membranes and potential obstructions by microclots or pathological blood components. Whether true myocyte hypoxia occurs to raise HIFs given these opposing mechanisms related to oxygen partial pressure in myocytes or whether ROS-induced (pseudo)hypoxia-signaling alone raises HIF-1α, remains unresolved. In either scenario, inhibition of PHDs would stabilize HIF-1α and raise its levels mainly locally.

7. The Status of Research on HIF-1α in Long COVID and ME/CFS

HIF-1α is a rapidly regulated intracellular transcription factor, not meant to be secreted; its half-life is only seconds to minutes (Gunton, 2020). As a result, measurements are difficult, unreliable and strongly influenced by methodological factors. HIF-1α was found increased in plasma in the acute infection despite the fact that it is an intracellular transcription factor, but mRNA was decreased (Wulandari et al., 2025). The available evidence points to a continuum of HIF-1α activation spanning acute COVID-19, Long COVID and finally ME/CFS. In the acute phase, HIF-1α stabilization is largely driven by systemic respiratory hypoxia. HIF-1α, its pathway and the gene expression, which it induces, is extensively discussed in review papers, mainly related to hypoxia during acute COVID-19 infection and the possible consequences for the development of PASC (da Silva et al., 2025), (Michalak et al., 2025). Thereafter, in the early phase of Long COVID, tissue hypoxia could be caused by disturbed (microvascular) perfusion (Kruger et al., 2024), (Pretorius et al., 2021), which would mainly affect skeletal muscle during exercise and, therefore, levels of HIF could rise locally. In ME/CFS, the predominant driver may be pseudohypoxia, arising mainly from ROS generated by mitochondrial dysfunction.

HIF-1α may play an early role in disease progression, beginning with acute lung infection and associated respiratory hypoxia (Guarnieri et al., 2023). Long COVID, HIF-1α levels may remain elevated in skeletal muscle, likely due to hypoperfusion-induced hypoxia driven primarily by

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microvascular dysfunction. This hypoxic environment, via upregulation of HIF-1α, may promote an early shift toward glycolytic metabolism in skeletal muscle during infection. The resulting proton load from anaerobic metabolism activates the sodium–proton exchanger (NHE1), which extrudes intracellular protons in exchange for sodium ions, leading to increased intracellular sodium concentrations (increased sodium influx) (Wirth & Löhn, 2024). If sodium efflux is simultaneously impaired during exercise potentially due to reduced Na^+/K^+-ATPase activity, intracellular sodium may accumulate further. Notably, key hormonal stimulators of Na^+/K^+-ATPase, which are needed for raising its activity during exercise, β2-adrenergic receptor signaling and calcitonin gene-related peptide (CGRP), appear to be deficient in ME/CFS, likely due to autoantibodies against the ß2-adrenergic receptor and its desensitization by a high sympathetic tone and small fiber neuropathy (lowering CGRP). Elevated intracellular sodium can reverse the direction of the sodium–calcium exchanger (NCX), resulting in calcium influx rather than efflux (Wirth & Löhn, 2024). The resulting calcium overload may contribute to mitochondrial dysfunction and ultimately lead to cellular injury in skeletal muscle as observed one day after an exercise test (Appelman et al., 2024).

Taken together, these observations suggest that HIF-1α activation follows a progressive transition: from systemic hypoxia to regional hypoperfusion-induced hypoxia, and ultimately to pseudohypoxia mediated by oxidative stress. To clarify a potential contribution of HIF-1α to ME/CFS pathophysiology, direct quantification in skeletal muscle, particularly following exercise, would be necessary.

8. Basement Membrane Thickening in Capillaries of Skeletal Muscle and Disturbed Angiogenesis: Roles of HIF-1α and HIF-2α

8.1. Potential Role of HIF-1α for Capillary Basement Membrane Thickening

After discussing connective tissue disorders related to ligament laxity, cervicocranial instability and orthostatic dysfunction and the pathomechanisms that potentially worsen the quality of the connective tissue in ME/CFS, this section will highlight basement membrane thickening in skeletal muscle capillaries and explore potential disturbances in angiogenesis.

Basement membrane thickening, characterized by excessive ECM deposition dominated by collagen IV, and amyloid accumulation have been reported in skeletal muscle capillaries of ME/CFS patients (Hejbøl et al., 2022), (Aschman et al., 2023), (Charlton et al., 2025), (Slaghekke et al., 2025). These alterations narrow the capillary lumen, impair perfusion and diffusion, and may promote or exacerbate tissue hypoxia. HIF-1α is a plausible stimulus of ECM accumulation. HIF-1α is a master regulator of hypoxic adaptation, and a major part of its function is to stimulate production of secreted factors that drive angiogenesis and ECM remodeling in a paracrine fashion. It stimulates ECM synthesis and is known to promote fibrosis in animal models (Haase, 2009). HIF-1α upregulates the production and release of profibrotic mediators such as CTGF, TIMP-1, and PAI-1 (Higgins et al., 2004), (Kietzmann et al., 1999). In diabetic nephropathy, the paradigm of capillary basement membrane thickening, HIF-1α activation contributes to ECM accumulation, driven by both hypoxia and ROS (Palm, 2006), (Takiyama & Haneda, 2014).

The shift toward more glycolytic muscle fibers and reduced mitochondrial mass in ME/CFS is contrary to HIF-2α effects but aligns with HIF-1α–mediated metabolic effects (Table 1). HIF-1α may also raise microvascular leakage together with other mediators/mechanisms like VEGF, cytokines, ROS and vasoactive mediators like bradykinin, histamine, prostaglandin E2 and adenosine and thus contribute to intravascular hypovolemia (Wirth, 2026).

8.2. Angiogenesis and Differential Contributions of HIF-1α and HIF-2α

ECM formation is an integral component of angiogenesis and is regulated by both HIF-1α and HIF-2α. While HIF-1α consistently promotes a glycolytic phenotype and primarily mediates acute, short-term responses to hypoxia such as the initiation of angiogenesis, HIF-2α is more involved in long-term adaptation, supporting vessel maturation and stabilization (Table 1).

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Metabolically, HIF-2α differs from HIF-1α by favoring oxidative phosphorylation, modestly promoting slow-twitch muscle fiber programs (mainly through indirect effects), and driving macrophage polarization toward a reparative M2 phenotype (Rasbach et al., 2010). In this way, HIF-2α helps maintain a cellular environment that supports efficient oxidative metabolism under (rather mildly) hypoxic conditions. In contrast, HIF-1α shifts metabolism toward glycolysis, reduces mitochondrial content, and promotes pro-inflammatory M1 macrophage activation. It decreases mitochondrial biomass by suppressing mitochondrial biogenesis, limiting mitochondrial utilization, and enhancing mitochondrial degradation through mitophagy (Semenza, 2012), (X.-B. Zhang et al., 2025).

The pattern of muscle biopsy findings in ME/CFS, more glycolytic fibers, reduced mitochondrial biomass, strongly suggests relative dominance of HIF-1α effects over HIF-2α signaling (Table 1). Decreased capillary density in skeletal muscle (Aschman et al., 2023), (Charlton et al., 2025), (Slaghekke et al., 2025) may indicate ineffective angiogenesis and raise the suspicion that this could be due to a deficiency of HIF-2α and an imbalance between HIF-1α and HIF-2α (initiation versus maturation of angiogenesis).

Three isoforms of HIF-inactivating PHDs have been reported. PHD2 is the main isoform in the inactivation of HIF-1α; PHD3 preferentially hydroxylates / inactivates HIF-2α (Appelhoff et al., 2004). By inhibiting PHDs, moderate levels of ROS do stabilize both HIF-1α and HIF-2α to raise their levels. While HIF-1α is held responsible for adaptation to acute hypoxia, HIF-2α is the dominant form of HIF in chronic hypoxia ((Steinberger & Eubank, 2023). The question arises why the pattern of findings in the chronic state of ME/CFS (Table 1) reflects the pattern of effects of HIF-1α of acute hypoxia, and not of HIF-2α which would be expected for the chronic situation of ME/CFS. A deficiency in HIF-2α may be explained by the fact high levels or bursts of ROS destabilize HIF-2α via calpain-dependent degradation, in which xanthin oxidase is involved, and via impaired translation. HIF-2α contains a calpain-sensitive domain (Nanduri et al., 2013). By contrast, HIF-1α is comparatively resistant. High levels or bursts of ROS could shift balance toward HIF-1α dominance. ROS could be produced during skeletal muscle work due to mitochondrial dysfunction; strong bursts of ROS could be generated during muscle work that cause PEM and skeletal muscle cell necroses (Appelman et al., 2024), (Scheibenbogen & Wirth, 2025). Excessive ROS worsens HIF-2α function, and impaired HIF-2α reduces mitochondrial protection. This can create a self-reinforcing dysfunction loop. Moreover, HIF-1α induces the expression of PHD3, which inactivates HIF-2α. Hence, both effects together could favor HIF-1α over HIF-2α in ME/CFS. Thus, despite PHD inhibition, under the influence of high ROS levels or bursts of ROS in ME/CFS, HIF-2α levels in the chronic course of ME/CFS may be insufficient, weakening angiogenesis maturation while elevated HIF-1α levels could continue stimulating both remodeling and initiation of angiogenesis including the production of basement membrane components.

9. The Potential Role of an Imbalance of HIF-1α and HIF-2α for Disease Chronification

The findings in skeletal muscle presented in Table 1 strongly argue against the presence of HIF-2α–mediated effects. An imbalance of HIF-1α over HIF-2α at all the stages of angiogenesis could disturb and stop the physiological maturation processes of angiogenesis and explain the paradoxical combination of reduced capillary density and excessive capillary basement membrane thickening. If present, an ineffective polarization of macrophages towards the M2 repair due to a deficient HIF-2α action may also impair skeletal muscle structure and function. It is conceivable that a relative predominance of HIF-1α over HIF-2α not only impairs angiogenic maturation but may also arrest the broader healing process at this stage. In addition, HIF-1α and HIF-2α exert distinct effects on skeletal muscle stem cells (satellite cells), which are essential for regeneration and repair. HIF-1α primarily promotes early satellite cell activation and glycolysis-driven proliferation, whereas HIF-2α supports stem cell maintenance and long-term regenerative capacity under hypoxic conditions (Liu et al., 2012), (Pircher et al., 2021). The increased proportion of glycolytic fibers and the reduced

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mitochondrial biomass observed in ME/CFS may also reflect an imbalance between HIF-1α and HIF-2α. In this context, diminished mitochondrial biomass may arise not only from direct mitochondrial damage but also from dysregulation, where a predominant influence of HIF-1α outweighs the opposing, pro-aerobic effects of HIF-2α. Mitochondrial damage, which may be associated with PEM, could lead to excessive ROS production, thereby impairing HIF-2α's ability to exert its regenerative functions and potentially contributing to the low rate of spontaneous recovery.

Maintaining an appropriate balance at every stage of the healing or regenerationi process between these HIF-factors appears particularly relevant in light of evidence for muscle damage and regeneration in biopsies from ME/CFS patients (Appelman et al., 2024). A transition from predominantly HIF-1α–mediated activity to HIF-2α–driven signaling is a critical step in the regenerative process ((Pawlik et al., 2024). However, this shift may be impeded by the greater susceptibility of HIF-2α to degradation during bursts of reactive oxygen species (ROS), which can arise from mitochondrial dysfunction, whereas HIF-1α appears comparatively resistant. A persistent HIF-1α dominance may therefore compromise regenerative capacity in the long run and impair tissue repair. Such dysregulations should be considered when addressing the persistently low healing rates observed in ME/CFS, despite the absence of irreversible organ damage or major genetic abnormalities, and with autoimmunity, one potential driver of chronicity, present perhaps only in half of the patients.

Hypoxia stabilizes both HIFs by decreasing activity of PHDs, whereas hyperoxia promotes their degradation (Kumar & Choi, 2015), (Albanese et al., 2020), (Kierans & Taylor, 2021). Hyperoxia generally suppresses both HIFs, but HIF-1α is typically inactivated more rapidly and completely than HIF-2α because it is more oxygen-sensitive (Keith et al., 2012), (Bakleh & Al Haj Zen, 2025). Thus, HIF-2α is less sensitive to degradation by oxygen through the action of PHDs while it is more sensitive against bursts of ROS than HIF-1α through the effect of calpain. These considerations could become important with regard to the potential mechanisms of improvement reported in studies using hyperbaric hyperoxic treatments (HBOT) for ME/CFS or long COVID (Katz et al., 2024), (Wu et al., 2024), (Hadanny et al., 2024), (Pawlik et al., 2024), (Kim et al., 2025). Apart from other favorable effects including anti-inflammatory effects and improvement of the metabolic situation (Pawlik et al., 2024), HBOT might thus improve the balance of both HIFs in favor of HIF-2α which is associated with regeneration. The question is whether hyperoxia can still exert a beneficial effect on the balance between the two HIF as one of its potentially favorable mechanisms once mitochondrial dysfunction has developed and ROS, rather than hypoxia, have become the predominant cause of PHD inhibition, as outlined above.

Measurements of both HIFs in skeletal muscles and other organs and the investigation of the polarization state of macrophages in biopsies would be very useful.

10. Summary

This publication deals with the frequent association of disturbed connective tissue and ME/CFS. The association between connective tissue weakness and its clinical manifestations including craniocervical instability, hypermobility, and orthostatic intolerance (linked to the connective tissue of capacitance vessels) as well as basement membrane thickening in muscular capillaries, may be explained by a unifying mechanism driven by hypoxia and ROS generated through mitochondrial dysfunction. Hypoxia or ROS-mediated inhibition of PHD enzymes reduces degradation of HIF-1α while impairing collagen cross-linking, thereby weakening connective tissue. Chronically elevated HIF-1α can further alter the composition of connective tissue in a manner that compromises its structural integrity. In parallel, mast cell overactivity may contribute to collagen destabilization through the release of chymase and tryptase, which activate matrix metalloproteinases (MMPs), while inflammatory cytokines may further upregulate MMP expression.

The resulting connective tissue impairment manifests clinically as ligamentous laxity, craniocervical instability, potentially exacerbated by concurrent skeletal muscle pathology. Furthermore, it can cause or exacerbate orthostatic dysfunction by impairing the quality of connective

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tissue of capacitance vessels. The resulting worsening of orthostatic function may be an important factor in the chronification of the disease by cardiac preload failure involved in hypoperfusion of skeletal muscle and brain and orthostatic stress. The considerations also help in understanding why patients with overt or latent preexisting connective tissue disorders are particularly affected by ME/CFS.

In capillaries of skeletal muscle of ME/CFS patients increased levels of HIF-1α might cause overproduction of extracellular matrix with basement membrane thickening creating a capillary diffusion and perfusion disturbance further worsening hypoxia. Sensitivity of HIF-2α to degradation via a ROS mediated mechanism leaves angiogenesis unfinished to explain decreased capillary density and overproduction of extracellular matrix. The metabolic profile observed in the skeletal muscle of ME/CFS patients marked by reduced mitochondrial biomass, a shift toward glycolytic fiber types, and increased extracellular matrix deposition suggests a predominance of HIF-1α–mediated signaling over HIF-2α activity, which would instead be expected to promote a more oxidative phenotype characterized by slow-twitch fibers and greater capillary density. Measurements of HIFs are difficult but are required to clarify the relationship.

11. Conclusions

There appears to be a bidirectional relationship between connective tissue disorders and ME/CFS: underlying connective tissue abnormalities may increase susceptibility to ME/CFS, while ME/CFS may, in turn, aggravate connective tissue pathology. ME/CFS via inhibition of PHDs and via the resulting HIF-1α could worsen the quality of connective tissue of ligaments and blood vessels to cause or worsen orthostatic dysfunction and cause skeletal muscle capillary membrane thickening and disturb angiogenesis maturation.

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