Hypothesis

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Connecting the Dots between Hypermobile Ehlers-Danlos-Syndrome, Abnormal Fascia, Lymphatic and Glymphatic System Impairment, Craniocervical Instability, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID

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Connecting the Dots Between Hypermobile Ehlers-Danlos-Syndrome, Abnormal Fascia, Lymphatic and Glymphatic System Impairment, Craniocervical Instability, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID

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Abstract

Interdisciplinary research is needed on the biomechanical and structural pathways that might explain why people with connective tissue disorders like hypermobile Ehlers-Danlos Syndrome (hEDS) are particularly susceptible to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and ME/CFS-like presentations of Long COVID. In particular, research is needed on the role that disordered fascia and lymphatic system dysfunction might play in the pathophysiology of ME/CFS and Long COVID. Research is also needed on the role that spinal conditions like craniocervical instability and Chiari Malformation might play in obstructing outflow from the glymphatic system.

Keywords: ME/CFS; lymphatic system; glymphatic system; fascia; hypermobile ehlers danlos syndrome; hypermobility spectrum disorders; craniocervical instability; chiari malformation

Why the Proposed Research is Needed

While definitions (and thus prevalence estimates) of Long COVID vary, one recent meta-analysis found the global prevalence of Long COVID among those with a COVID-19 infection to be 36% (1). About half of the individuals with Long COVID appear to meet or substantially approximate the criteria for ME/CFS (2). Even if these estimates were double the actual rates, the number of people with an ME/CFS-like presentation of Long COVID would still be extremely high. Studies of the global prevalence of ME/CFS prior to Long COVID estimated prevalence at between 0.2% and 2.8% -- a smaller proportion but nevertheless many millions of people [3].

My coauthors and I recently published research finding that people with generalized joint hypermobility (and especially people with extreme hypermobility) are at higher risk of Long COVID [4]. Hypermobility is also common among people with ME/CFS. One study found that about half of individuals with ME/CFS referred to a specialty clinic in Sweden had hypermobility, using thresholds tied to the highest 5% for their age and gender group [5]. One in five had a diagnosis of hEDS, many times the estimated prevalence in the general population. The same study also found a large share of individuals had craniocervical obstructions.

While there has been some analysis of why people with hEDS may be particularly vulnerable to ME/CFS (see citations collected here [4]), the relationship is understudied. This is unfortunate as an improved understanding could not only help a significant subset of the population of people diagnosed with ME/CFS and Long COVID but also possibly generate learning that could help others.

My Experience as a Patient Caregiver

I am motivated to study the relationship of hEDS to ME/CFS by personal experience; my daughter has been diagnosed with hEDS, ME/CFS, and a range of other conditions. Through the

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experience of eight years of caring for her, I can attest that biomechanical and structural issues loom large in her presentation. At 16, she required surgery for tethered cord syndrome and was scheduled to have surgery to treat CCI and Chiari Malformation when the COVID-19 pandemic broke out. Her bones regularly go out of place, leading to muscle spasms that appear to spread through the fascia. Fascial tightness in the skull and around the axillary and popliteal nodes appears to be associated with impaired lymphatic drainage, as suggested by symptoms that improve when the tightness is alleviated and we undertake manual lymphatic drainage. These include a localized sensation of trapped fluid and (when untreated or undertreated) systemic symptoms of increased fatigue and overall malaise.

While it is certainly possible that these kinds of biomechanical and structural issues have little to do with the elevated risk of ME/CFS and Long COVID among people with hEDS, this seems unlikely to me. At a minimum, these pathways should be prominent targets for research.

Fascia-Mediated Constraints on Lymphatic Function: A Potential Contributor to ME/CFS?

Abnormalities in the fascia of people with hEDS and Hypermobility Spectrum Disorders (HSD) provide a potential mechanism through which these connective tissue disorders could contribute to ME/CFS symptoms. One recent paper found "increased fascial thickness, reduced glide between fascial planes, and altered tissue stiffness" among people with HSD/hEDS and discusses a potential mechanism (elevated TGF-β1) through which these abnormalities could contribute to chronic fatigue [6]. There are a number of other processes through which impaired fascia could potentially contribute to symptoms in people with HSD/hEDS [7]. In particular, given that lymphatic vessels are located within the fascia [8] and abnormal fascia functioning could affect lymphatic flow [9], I would encourage exploration of the possibility that impaired lymphatic functioning contributes to ME/CFS symptoms in people with HSD/hEDS.

One potential pathway through which impaired lymphatic function could contribute to some of the symptoms seen in people with ME/CFS and ME/CFS-like presentations of Long COVID begins with vascular damage and/or inflammation stemming from a virus, a systemic inflammation event (such as a mast cell activation or ischemia/reperfusion) or exposure to an environmental irritant. This significantly increases vascular permeability, leading to an influx of protein-rich fluid into the interstitium [10]. If thick and disordered fascia disrupt the efficient functioning of the lymphatic system, it may be unable to remove all the extracellular matrix (ECM) fragments produced during vascular repair, potentially contributing to a chronic state of low-grade inflammation and endothelial activation and dysfunction that may delay or impair the completion of the vascular repair and the efficient removal of pro-inflammatory cytokines [9,11]. This is consistent with the findings of elevated proteins associated with vascular repair in proteomic studies of people with ME/CFS [12]. The ECM fragments themselves may contribute to further lymphatic dysfunction [13], as would physical inactivity related to the patients' illness, further reinforcing the feedback loop. Increases in vascular filtration during physical or mental exertion could exacerbate the problem by significantly increasing the volume of protein-rich fluid entering the interstitium and the amount of proteins needing drainage through an impaired lymphatic system [14]. This could potentially play a role in post-exertional symptom exacerbation and post-exertional malaise.

There may be other factors not related to connective tissue orders that contribute to lymphatic system dysfunction. For example, researchers report that during acute vascular permeability, fibrinogen released into the interstitium converts to fibrin which forms a gel that impedes lymphatic drainage [15]. But what happens when that fibrin has amyloid properties, as we see with micro clots in ME/CFS and Long COVID [16]? Could amyloid fibrin be clogging both the vascular and lymphatic systems? Fibrin clots have been found in the pulmonary lymphatic vessels of individuals who died following severe COVID-19 [17]. A study of 25 patients with Long COVID and 21 controls found a greater concentration of amyloid-containing deposits in the muscles of Long COVID patients, but in the ~2 cm muscle sections biopsied, these deposits were not located in capillaries or lymphatic vessels

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but rather next to capillaries and in the extracellular matrix between muscle fibers [17]. The deposits increased in both controls and patients with Long COVID after exercise, which is consistent with the hypothesis that they are present in the interstitium due to vascular filtration during exercise. This study does not provide support for amyloid deposits clogging the observed lymphatic vessels, but the researchers sampled only a tiny section of the vast network of lymphatic vessels, so there could potentially be amyloid fibrin clots elsewhere in the lymphatic system. If their lymphatic systems are impaired, the Long COVID patients may struggle to remove both amyloid fibrin deposits and other proteins that enter the interstitium with plasma during exercise.

Significant increases in protein-rich interstitial fluid not cleared by the lymphatic system can also contribute to the formation of subcutaneous adipose tissue in some individuals, as is believed to happen in lipedema, which is pro-inflammatory and can become fibrotic and painful, potentially contributing to pain and ongoing inflammation in people with ME/CFS [18,19].

Potential Contribution of the Glymphatic System to ME/CFS and Long COVID

A notable exception to the relative neglect of biomechanical pathways in the study of ME/CFS and Long COVID is research on the glymphatic system. Several studies have found abnormal glymphatic system dysfunction in people with Long COVID [20,21], and a recent hypothesis paper explored the potential for glymphatic dysfunction to contribute to ME/CFS [22] symptoms. As this research proceeds, it will be important to consider whether spinal conditions like craniocervical instability and Chiari malformation, potentially compounded by mechanical narrowing tied to tightness of the deep cervical fascia, could impede the removal of glymphatic fluid and drainage of CSF through vessels passing through the craniocervical junction as first suggested here [4]. Potentially, people with these spinal conditions might not experience symptoms until the volume of protein-rich fluid entering the interstitium (for example, in perivascular spaces, the subarachnoid region, and the dural venous sinuses) markedly increases following vascular damage or increased inflammation. When this occurs, congestion at the craniocervical junction may contribute to excess glymphatic fluid build-up, which causes increases in intracranial hypertension and brainstem compression. (A newly published article offers a different mechanical hypothesis linking spinal abnormalities to brainstem compression in people with ME/CFS [23]. It could be useful to integrate these hypotheses.)

It is also possible that blockages in the lymphatic system can affect the glymphatic system more directly. More research is needed on the connection between the two drainage systems. For example, a recent mouse model study found that noninvasive stimulation of superficial lymphatics through the skin doubled outflow of cerebrospinal fluid (CSF) [24].

Lymphatic Inflow and Outflow—A Potential Conceptual Framework

One way to conceptualize the relationship of the lymphatic and glymphatic systems to ME/CFS and Long COVID is to focus on assessing the extent of, and factors contributing to: (a) excess inflow of fluid into the interstitium and (b) impaired removal of that fluid. On the inflow side, it will be important to understand whether and to what extent (and why) there is a large increase in the volume of fluid entering the interstitium that overwhelms the lymphatic system of people with ME/CFS (e.g., due to inflammation, vascular damage, or both). There are many factors that could impair the removal of interstitial fluid by the lymphatic system including the fascial abnormalities, ECM fragments, fibrin gel and structural spinal disorders discussed above. Research into treatments could consider how to staunch the inflow of fluid and improve its drainage. Manual lymphatic drainage is one of a number of strategies for improving lymphatic flow whose efficacy could be studied [25].

Finally, research is needed on how the pathways discussed above interrelate with other disease pathways in ME/CFS and Long COVID, such as autoantibodies and microclots.

There are many other hypotheses that could be explored, but hopefully this discussion is sufficient to underscore the importance of conducting additional research into the role that fascial

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abnormalities and lymphatic system dysfunction play in the development of ME/CFS and Long COVID among people with hEDS and HSD.

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Abbreviations

The following abbreviations are used in this manuscript:

CSF	Cerebrospinal Fluid
ECM	Extracellular matrix
hEDS	Hypermobile Ehlers-Danlos Syndrome
HSD	Hypermobility Spectrum Disorders
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

References

1. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global Prevalence of Long COVID, Its Subtypes, and Risk Factors: An Updated Systematic Review and Meta-analysis. Open Forum Infect Dis. 2025 Sept 1;12(9):ofaf533.
2. Dehlia A, Guthridge MA. The persistence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) after SARS-CoV-2 infection: A systematic review and meta-analysis. J Infect [Internet]. 2024 Dec 1 [cited 2025 Dec 23];89(6). Available from: https://www.journalofinfection.com/article/S0163-4453(24)00231-7/fulltext
3. Tschopp R, König RS, Rejmer P, Paris DH. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A preliminary survey among patients in Switzerland. Heliyon [Internet]. 2023 May 1 [cited 2025 Dec 23];9(5). Available from: https://www.cell.com/heliyon/abstract/S2405-8440(23)02802-5
4. Torok, Regina A, Lubell, Jeffrey, Rudy, Rena M, Eccles, Jessica, Quadt, Lisa. Variant connective tissue as a risk factor for long COVID: a case-control study of data from a retrospective online survey of adults in the USA and UK. BMJ Public Health [Internet]. 2025 Sept 17 [cited 2025 Dec 2];3(2). Available from: https://doi.org/10.1136/bmjph-2025-002949
5. Bragée B, Michos A, Drum B, Fahlgren M, Szulkin R, Bertilson BC. Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Neurol [Internet]. 2020 Aug 28 [cited 2025 Dec 2];11. Available from: https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2020.00828/full
6. Wang TJ, Stecco A, Hakim AJ, Schleip R. Fascial Pathophysiology in Hypermobility Spectrum Disorders and Hypermobile Ehlers–Danlos Syndrome: A Review of Emerging Evidence. Int J Mol Sci. 2025 Jan;26(12):5587.
7. Slater AM, Barclay SJ, Granfar RMS, Pratt RL. Fascia as a regulatory system in health and disease. Front Neurol [Internet]. 2024 Aug 7 [cited 2025 Dec 2];15. Available from: https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2024.1458385/full
8. Albertin, Giovanna, Astolfi, Laura, Fede, Caterina, Simoni, Edi, Contran, Martina, Petrelli, Lucia, et al. Detection of Lymphatic Vessels in the Superficial Fascia of the Abdomen. Life. 2023;13(3):836.
9. Tuckey B, Srbely J, Rigney G, Vythilingam M, Shah J. Impaired Lymphatic Drainage and Interstitial Inflammatory Stasis in Chronic Musculoskeletal and Idiopathic Pain Syndromes: Exploring a Novel Mechanism. Front Pain Res [Internet]. 2021 Aug 23 [cited 2025 Dec 2];2. Available from: https://www.frontiersin.org/journals/pain-research/articles/10.3389/fpain.2021.691740/full
10. Arroyo AG, Iruela-Arispe ML. Extracellular matrix, inflammation, and the angiogenic response. Cardiovasc Res. 2010 May 1;86(2):226–35.

 doi:10.20944/preprints202512.1222.v3

11. Zhang P hong, Zhang W wu, Wang S shun, Wu C hua, Ding Y dong, Wu X yi, et al. Efficient pulmonary lymphatic drainage is necessary for inflammation resolution in ARDS. JCI Insight [Internet]. 2024 Jan 9 [cited 2025 Dec 22];9(1). Available from: https://insight.jci.org/articles/view/173440
12. Heng B, Gunasegaran B, Krishnamurthy S, Bustamante S, Pires AS, Chow S, et al. Mapping the complexity of ME/CFS: Evidence for abnormal energy metabolism, altered immune profile, and vascular dysfunction. Cell Rep Med [Internet]. 2025 Dec 16 [cited 2025 Dec 22];6(12). Available from: https://www.cell.com/cell-reports-medicine/abstract/S2666-3791(25)00587-7
13. Czarnowska E, Ratajska A, Jankowska-Steifer E, Flaht-Zabost A, Niderla-Bielińska J. Extracellular matrix molecules associated with lymphatic vessels in health and disease. Histol Histopathol. 2023;39(01):13–34.
14. Korthuis RJ. Microvascular Fluid and Solute Exchange in Skeletal Muscle. In: Skeletal Muscle Circulation [Internet]. Morgan & Claypool Life Sciences; 2011 [cited 2025 Dec 22]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK57134/
15. Nagy JA, Benjamin L, Zeng H, Dvorak AM, Dvorak HF. Vascular permeability, vascular hyperpermeability and angiogenesis. Angiogenesis. 2008 June 1;11(2):109–19.
16. Nunes JM, Kruger A, Proal A, Kell DB, Pretorius E. The Occurrence of Hyperactivated Platelets and Fibrinaloid Microclots in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Pharmaceuticals. 2022 Aug;15(8):931.
17. Appelman B, Charlton BT, Goulding RP, Kerkhoff TJ, Breedveld EA, Noort W, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. Nat Commun. 2024 Jan 4;15(1):17.
18. Allen M, Schwartz M, Herbst KL. Interstitial Fluid in Lipedema and Control Skin. Womens Health Rep. 2020 Oct 14;1(1):480–7.
19. Herbst KL. Subcutaneous Adipose Tissue Diseases: Dercum Disease, Lipedema, Familial Multiple Lipomatosis, and Madelung Disease. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2025 Dec 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK552156/
20. Wu L, Zhang Z, Liang X, Wang Y, Cao Y, Li M, et al. Glymphatic system dysfunction in recovered patients with mild COVID-19: A DTI-ALPS study. iScience [Internet]. 2024 Jan 19 [cited 2025 Dec 23];27(1). Available from: https://www.cell.com/iscience/abstract/S2589-0042(23)02724-4
21. Zhou Z, Zhao T, Sekendiz Z, Kritikos M, Fontana A, Clouston S, et al. Impaired Cerebrospinal Fluid 18F-FEPPA Clearance in Long COVID Suggests Altered Glymphatic System Function. J Nucl Med. 2024 June 1;65(supplement 2):242407–242407.
22. Nemat-Gorgani M, Jensen MA, Davis RW. Glymphatic System Dysregulation as a Key Contributor to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Int J Mol Sci. 2025 Jan;26(23):11524.
23. Wood JD, Varley TF, Hartman J, Melia N, Kaufman DL, Falor T. Brainstem dysfunction as a potential etiology of ME/CFS and long COVID: A mechanical basis. Med Hypotheses. 2026 Jan 1;206:111812.
24. Jin, Hokyung, Yoon, Jin-Hui, Hong, Seon Pyo, Hwang, Yu Seok, Jin Yang, Myung, Choi, Jieun, et al. Increased CSF drainage by non-invasive manipulation of cervical lymphatics | Nature. Nature. 2025;643:755–67.
25. Riste L, Perrin R, Mulholland T, Hann M, McDonald O, Heald A. Testing the Feasibility of a Self-Help Intervention That Includes Lymphatic Drainage to Reduce Fatigue-Related Symptoms Among Patients with Long COVID in General Practice: Experiences from Our Randomized Controlled Trial (RCT). Infect Dis Ther [Internet]. 2025 Dec 24 [cited 2026 Jan 2]; Available from: https://doi.org/10.1007/s40121-025-01287-z