Joint Hypermobility Syndrome and Complex Illness: The Extracellular Matrix Connection

by Michael McEvoy, www.MetabolicHealing.com

Joint hypermobility syndrome (JHS) is a significantly under-reported clinical phenomenon. Individuals with JHS frequently present with a complex array of symptoms and conditions. These often include postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), neurological symptoms, heart rate changes, blood pressure fluctuations, chronic pain, frontal, temporal and occipital headaches, visual disturbances, blood clotting abnormalities, vascular and circulatory conditions, bruising, organ prolapse, bowel disorders, esophageal, cardiac and pyloric valve abnormalities, autoimmune conditions, chiari malformation, cranial cervical instability, intracranial pressure changes, disturbances of cerebrospinal fluid, dura matter abnormalities, post-traumatic stress disorder (PTSD) and sensory processing disorders, anxiety, depression, and gynecological issues such as polycystic ovary syndrome (PCOS) and endometriosis.

The etiologies of the complex symptom presentations that are associated with JHS have been explored to a limited extent. By understanding these etiologies, it is possible to develop therapeutic interventions for individuals suffering with these conditions.

Loss of Extracellular Matrix (ECM) Function

"Strictly speaking, the cell concept is only a morphological abstraction. Seen biologically, it cannot be accepted without the vital environment of the cell," says Alfred Pischinger, MD, in his book *Matrix & Matrix Regulation: Basis for a Holistic Theory in Medicine.*

It can be argued that the extracellular matrix (ECM) is the most overlooked aspect of human physiology, yet one that may hold the key to unravelling the complexities of chronic disease. Joint hypermobility syndrome, such as EDS (Ehlers-Danlos syndrome), explicitly implicates disruptions to the normal functions of the ECM. The ECM is a vast and complex network – comprised of collagen, proteins, polysaccharides, and electrolyte fluids – with the following essential functions:

- To provide the structural scaffolding for cells and organs,
- To modulate cell-to-cell communication,
- To modulate the life cycle of cells,
- To create a yin/yang balance between cell survival and cell death,
- To modulate growth factor and cytokine function and signaling,
- To regulate stem cell function, and
- To provide the proper fluid balance and pressure gradients in various tissue compartments.

Regulation of Growth Factors

With the loss of normal ECM function, a number of pathological processes and complex symptoms prevail. Cells maintain their adhesion to the ECM through surface interfaces such as integrins and basement membrane laminins. Cells that lose their adhesion to the ECM undergo a form of cell-programmed death.

A number of critical growth factors bind to and are activated by the ECM. These include VEGF-A and VEGF-B (vascular endothelial growth factor A & B), FGF-2 (fibroblast growth factor-2), IgF (insulin growth factor), HGF (hepatocyte growth factor), PDGF-BB (platelet-derived growth factor BB), EGFR (epidermal growth factor) and TGFß-1 (transforming growth factor ß-1).[1] Insufficient collagen and proteoglycans in the ECM will directly impair the function of these important growth factors, leading to a number of adverse, downstream effects.

VEGF-A is the primary operator in angiogenesis and is critical in neuronal function, wound repair, endothelial cell function, and in the delivery of oxygen to tissues. Individuals with JHS frequently suffer from organ and vascular fragility, skin bruising, epilepsy, and neuropathy as well as chronic pain. Domains located within the TNXB gene have been found to regulate the maturation and function of VEGF-A, VEGF-B, and TGFß.[2,3] Mutations and deletions of TNXB will impair the function of these critical growth factors and increase the probability of vascular, endothelial, and neuronal conditions. Mutations and deletions of the TNXB gene (tenascin-X) lead to a form of hypermobile EDS.

TGFß-1 is a critical cytokine growth factor that requires a functional ECM for activation. Since the 1980s it has been known that forms of EDS and Marfan syndrome frequently feature higher blood levels of TGFß-1.[4,5] Among its

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myriad number of functions, TGFß-1 is a potent pro- and anti-inflammatory cytokine, activating certain mature T-cells (including anti-inflammatory T-regs) and is necessary for cell growth and proliferation, neuronal refinement, synaptic pruning, as well as stem cell differentiation. TGFß is also a key regulator of the gut and is released by numerous GI cells, such as dendritic cells and epithelial cells.[6]

The loss of normal function of TGFß-1 due to ECM dysfunction may in part explain the higher frequency of autoimmune and rheumatic diseases seen among those with JHS, as well as the frequency of gastrointestinal symptoms and gynecological conditions such as endometriosis.[7] Endometriosis in particular has a pathophysiology that directly involves aberrant TGFß-1 and VEGF-A signaling.[8,9]

Brain structural abnormalities and associated anxiety disorders in JHS have been observed.[10] TGFß signaling is critical for axonal function in the developing brain,[11] including neurite development in the hippocampus, as well as for stem cell differentiation and function during embryogenesis. Mouse studies have found that the inactivation of TGFß receptors in the mid-hind brain regions result in enlarged midbrain.[12] Aberrant TGFß signaling in the developing brain, due to inadequate ECM function, may provide a hypothesis for the brain structure abnormalities observed in EDS and JHS, as well as the associated amygdala volume differences, anxiety, and emotional processing disturbances seen among those with JHS.[10]

From the therapeutic side, CBD (cannabidiol) has been shown useful for JHS individuals suffering with anxiety. This may in part be explained by the fact that the amygdala is rich in endocannabinoid receptors. LDN (low dose naltrexone) has reportedly been used for emotional processing therapies with varied success. Pharmaceuticals such as losartan and VIP (vasoactive intestinal polypeptide) have been used to lower high levels of TGFß-1.

IgF-1 (insulin growth factor-1) regulates the activities of growth hormone (GH). Very few conditions feature elevations in IgF-1, but EDS and JHS are among these.[13,14] IgF-1 is a potent promoter of type 1 and 3 collagen biosynthesis, as well as of the ECM-essential enzymes lysyl oxidase and lysyl hydroxylase.[15] What is critical to understand is that integrins (adhesive proteins that attach cells to the ECM) are centrally involved in the activation of IgF-1.[16] Among those with JHS, this implicates poor utilization of IgF-1 and the associated loss of cellular adhesion to the ECM as a focus for this growth factor's elevations.

Additional attention should address the need to support and optimize collagen turnover. Sodium ascorbate has shown to be useful in JHS, as vitamin C plays a decisive role in collagen and ECM synthesis and remodeling.

Idiopathic intracranial hypertension (IIH) is one of the most complex conditions associated with JHS and EDS. Individuals with IIH frequently suffer from cerebrospinal fluid leaks, severe headaches, visual field defects, palsy of cranial nerves, tinnitus, intracranial noises, and papilledema. The literature reports the association between IIH, elevated IgF-1 levels, and growth hormone therapy (as a trigger for IIH).[14,17] The somatostatin analogue drug octreotide (which inhibits growth hormone & IgF-1) was shown to significantly improve the symptoms of IIH in a case study of a patient with JHS.[14]

Therapeutically speaking, the modulation of growth factors presents a challenge because of underlying ECM structural defects. One of the overall adverse effects of growth factor dysregulation is related to loss of mTOR signaling. mTOR (mammalian target of rapamycin) is an intracellular protein that regulates numerous pathways related to cell growth, autophagy, immune cell modulation, and the inflammatory process. mTOR signaling has been detected in matrix-producing fibroblast cells and is highly responsive to growth factor activation. Insufficient amino acids have been shown to shift the mTOR program towards an inflammatory state through the activation of NF kappa-ß, whereas increased amino acids shift to a cell survival state via STAT1 genes.[18] One potential therapy in addition to mTOR-responsive amino acids (glutamine, arginine, leucine) could be the phospholipid phosphatidic acid (PA). Not only does PA promote mTOR, it behaves similar to growth factors and has been shown to increase the ECM constituent hyaluronic acid.[19] mTOR needs to be kept in balance with a related protein, AMPK. Experimental, injectable peptides such as BPC-157 are reportedly improving tissue recovery processes and may hold significant potential for JHS-related ECM dysfunction.

Additional attention should address the need to support and optimize collagen turnover. Sodium ascorbate has shown to be useful in JHS, as vitamin C plays a decisive role in collagen and ECM synthesis and remodeling. Maintenance of proper hydration and electrolyte balance is also crucial.

Polysaccharides are the fundamental sugars that serve as the basis of glycoproteins in the ECM, and various polysaccharide-containing supplements have been attempted with varying degrees of success. These include aloe vera, lion's mane, and maitake mushroom, as well as brown algae and red algae. In some cases, polysaccharides seem to reduce joint hyperextensibility. There have been isolated case reports of rapid tissue healing phases induced by sulfated polysaccharide-containing red algae, notably in JHS-associated bowel conditions. Aloe vera polysaccharides have been reported in some instances to improve bruising symptoms, rosacea, reduce hyperextensible joints, and some evidence suggests alteration of clotting factors.

MCAS, the ECM, and Joint Hypermobility

The fact that mast cell activation syndrome (MCAS) is commonly seen in JHS and EDS is no surprise.[20] Mast cells are clustered abundantly throughout loose connective tissues. Mast cells are most notable for their ability to degranulate and release histamine via IgE-mediated responses, although this is only a part of the story.

Mast cells are also reservoirs of heparin, an ECM proteoglycan that acts as an anticoagulant. Significantly, mast cells are integral to the normal function and repair processes of the ECM. The fact that mast cells have the ability to release fibroblast growth factors and heparin-binding epidermal growth factors (as well as to stimulate these in nearby fibroblasts) is significant because it illustrates the intrinsic relationship between mast cells and ECM-producing fibroblasts. Moreover, histamine acts to up-regulate the fibroblast growth factor-7 receptor via H1 receptors, while tryptase (an enzyme that is released with histamine and is associated with MCAS) has been shown to stimulate fibroblast growth factor-2 from fibroblasts.[21]

Is it possible that MCAS is actually a coordinated attempt to increase the production of collagen and ECM constituents? Is this a repair process gone wrong among those with JHS and EDS? What's clear is that the study of MCAS must take into consideration the relationship between mast cells, fibroblasts, and the conditions of the ECM environment.

While medications such as ketotifen, cromolyn sodium, and supplements such as quercetin have been useful at controlling MCAS symptoms, these substances don't address the cross talk between mast cells and the ECM environment. The ECM glycosaminoglycan chondroitin sulfate holds promise for MCAS, as it has been shown to be a potent inhibitor of connective tissue mast cells.[22] Evidence has shown that Nrf2 pathway activation may be a key intracellular modulator of mast cell degranulation.[23] Two recent case studies demonstrated stabilization of MCAS symptoms and associated control of histamine liberation with Nrf2 pathway activation using Nrf2-promoting supplements.

Environmental Toxins and the ECM

If individuals have a compromised ECM, they may be more prone to the destructive effects of toxins, certain drugs, and infections. Various pathogens including viruses, Lyme, mold, and bacteria lead to the infiltration of pro-inflammatory metalloproteinases (MMPs), which incite a breakdown of the ECM, leading to the infiltration of inflammatory cytokines and immune cells.[24] This process is likely a significant contributing factor to the collagen

deficiency complications among those with JHS due to their already weak ECM. Numerous case study reports among those with JHS and EDS identified fluoroquinolone antibiotics as being pivotal to patients' downward spiral into chronic illness; these drugs incite destructive effects on the ECM and connective tissue.[25]

cytokines IL1ß and IL18 and the activation of downstream cytokines such as NF kappa-ß and IFN-γ. Inflammasome activation is a significant contributing factor to autoimmune disease, including rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's)[27] as well as inflammatory bowel diseases such as Crohn's.[28]

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Positively charged, cationic toxic metals (such as aluminum, mercury and cadmium) may find their way to the ECM, where they attract to the negatively charged anionic sulfates in ECM glycosaminoglycans (GAGs). Stephanie Seneff's postulation that the herbicide glyphosate replaces glycine is highly relevant because glycine is the primary amino acid in collagen. The collateral damage of the metalloproteinase/toxicity-removal process is the degraded fragments of ECM constituents such as hyaluronic acid, teanscin-c, decorin, biglycan, and aggrecan.[26] These ECM fragments are known as DAMPs (damage associated molecular patterns). DAMPs trigger toll and NOD-like receptors (TLRs and NODs) and stimulate inflammasomes in macrophages, setting the stage for autoimmune processes.

Inflammasomes and Autoimmune Disease

Inflammasomes are intracellular protein complexes located within immune cells such as tissue macrophages. Inflammasomes are sensitive to a number of toxic and pathogenic stimuli such as PAMPs (pathogen associated molecular patterns), toxins (aluminum, cadmium, mercury, silicon dioxide, asbestos) as well as DAMPs. Inflammasome activation generates pro-inflammatory

The association between EDS, JHS, pain disorders, and rheumatic diseases is well established. A study of 66 women with fibromyalgia identified 27% as having joint hypermobility.[29] A study of 100 patients diagnosed with rheumatoid arthritis (RA) found 18% had joint hypermobility. All were female, and hypermobile patients had higher levels of PGE2 prostaglandins and IL-8.[30] A study of 81 patients diagnosed with SLE (systemic lupus erythematosus) found 48% had joint hypermobility, compared to 15% of the control group.[31] A study of 83 patients with inflammatory bowel disease and 67 healthy controls investigated the presence of JHS. Joint hypermobility was identified in 70.7% of Crohn's disease patients, compared to 25.4% of healthy controls.[32]

From clinical observations, many other autoimmune conditions frequently feature JHS but are significantly under-reported in the literature. From a therapeutic side, it is imperative to reduce the toxic burden in JHS patients.

In addition to the benefits of whole food, elimination-type diets for autoimmune conditions and targeting GI function, inflammasome activity can be curtailed through ß-hydroxybutyrate, a ketone. Research also finds that activating the AMPK protein can reduce expression of inflammasome activity. This can be accomplished in many different ways, such as through caloric restriction, exercise, and through supplements such as berberine, lipoic acid, and resveratrol.

Hypermobility Syndrome: Chronic Pain and Headaches

Chronic head and neck pain is common in JHS. Causes include chiari malformation, dura matter abnormalities, intracranial pressure, and CSF leaks.

Chiari malformation is a structural condition where the cerebellum protrudes into the spinal canal. A theory postulated by Driscoll suggests, in some cases of EDS, increased CSF pressure in the subarachnoid space (an area between the brain and the dura matter) can increase the prevalence of chiari; and by reducing this pressure, chiari can be reduced.[33] This intracranial pressure not only creates pain, it contributes to dysautonomia, CSF leaks, and papilledema (swelling of the optic nerve). The drug acetazolamide has been shown to improve this buildup of pressure. Already discussed is the potential use of the drug octreotide, in cases where IIH is caused by elevated IgF-1. Pain among those with JHS can be influenced by temperature, altitude, and barometric pressure. Upper cervical chiropractic care, cranial osteopathy, craniosacral therapy, CBD, and herbs like *Mitragyna speciosa* have been useful in managing some of these complications.

It has been observed that dystonia exists in roughly 66% of EDS patients.[34] Dystonia is characterized as involuntary muscle contractions that cause writhing and twitching. The cause of dystonia in EDS and JHS is linked to hypoperfusion and/or low oxygen levels. This is supported by the fact that dystonia has improved with oxygen therapies, as well as compression therapy.[34] Low doses of the drug L-DOPA (180 mg daily) have been shown effective in controlling dystonia in EDS.[34] Those who responded well to the L-DOPA treatment had an 82% improvement in dystonia symptoms and 59% of those had dramatic improvements. Dopamine at lower concentrations is a known vasodilator. Dopamine promotion therapy can be supported through natural products

such as the combination of *Mucuna pruriens* and vitamin B6, or tyrosine and B-6.

Genetics and Associated Comorbidities

Genomic variations of the RCCX gene cluster on chromosome 6 are likely a significant factor in the etiology of many patients with JHS and the associated comorbidities. The genes that comprise RCCX are very significant and confer powerful effects throughout the body. The RCCX gene cluster on chromosome 6 has been described as the most complex region within the human genome because many anomalous events occur in this region: unequal crossover, non-allelic homologous recombination (NAHR), duplications of genes, pseudogenes, overlapping gene regions, retroviral and transposon insertions, and intergenic recombination.

Briefly, the RCCX gene cluster consists of the following genes:

- TNXB (tenascin-X) is an anti-adhesive glycoprotein in the extracellular matrix. Deficiencies of TNXB cause a form of EDS that is associated with JHS and skin hyper-elasticity. New TNXB research finds associations with organ prolapse and bowel diseases.
- CYP21a2 makes adrenal hormones cortisol and aldosterone, which are critical in the stress response and in salt balance. Variations of CYP21a2 are linked to CAH (congenital adrenal hyperplasia), hirsutism, PCOS/ ovarian cysts, PTSD, abnormal stress response, and possibly psychiatric illness.
- C4 is central to the complement, innate immune system. C4 also is involved in the synaptic pruning process in the brain. Genetic variations and deficiencies of C4 are found in many types of autoimmune diseases: lupus, RA, celiac, Crohn's, ankylosing spondylitis, Grave's, and type 1 diabetes. Variations of the C4 gene have also been observed in autism and schizophrenia. The C4 gene contains an endogenous retrovirus, HERV-K. This retrovirus is known to be expressed in neurological diseases and in cancer.
- STK19's (formerly known as RP1) function is unknown.

Gene sequencing for RCCX is not yet commercially available. The RCCX genes can be thought of as a domino effect: when one gene is affected, they all are. Individuals with JHS plus comorbidities associated with RCCX (congenital adrenal hyperplasia, C4-associated autoimmune disease, PCOS, family history of mental illness) may very well have inherited an undesirable genotype.

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Michael McEvoy is the founder of MetabolicHealing.com. He's a clinician and educator who has created functional medicine-based platforms, which integrates modern health data analysis with evidence-based therapeutic interventions. Michael is a systems creator, integrator, and synthesizer of diverse clinical modalities.

Through unique educational and teaching endeavors, Michael's objective is to assemble a network of the world's top clinicians to meet the demands and challenges of 21st century functional medicine and to implement the analytical tools and frameworks required.