Chapter 2
Understanding Connective Tissue

Take Home Messages from this Chapter

- Hypermobility spectrum disorders and Ehlers-Danlos syndromes are genetic connective tissue disorders that impact connective tissue throughout the body. Connective tissue is found throughout all the systems of the body. Individual experiences, exposures, and genetics will impact the presentation and severity of connective tissue disorders.

- Collagen gives connective tissue its strength. Collagen is the scaffolding that structurally supports connective tissue. The production of collagen can be affected through a variety of different mechanisms. Different genetic variants are responsible for the specific deficits that define the different connective tissue disorders.

- Collagen exists in the extracellular matrix (ECM). The ECM consists of the space outside of the cells of the body. The ECM consists of proteins that determine the function of the connective tissue. Dysfunction of the collagen or the proteins in the ECM will cause the ECM to function less efficiently. In the ECM, many of the body's cellular processes occur that maintain homeostasis. A dysfunctional ECM will contribute to an overall poorer health presentation.

- The ECM can also be influenced — positively or negatively — by our own actions and exposures. Unfortunately, negative exposures are quite common and include: illness, toxins, poor lifestyle habits (food, sleep, stress, etc.), and past trauma of any type. Positive influences on the ECM include healthy lifestyles, appropriate individual food choices, adequate sleep, regulating and mitigating stress episodes, etc.

- The ECM communicates with other systems, helping to eliminate toxins and waste products, assisting with cell nutrition and hormonal regulation, supporting the regulation of the nervous and vascular systems, and regulating the inflammatory responses in the body. If there are issues in the structure of the ECM, as often exist with connective tissue disorders, any or all of these roles may be compromised.

- Patients with connective tissue disorders may be more vulnerable to negative influences on the ECM. As a result, these individuals may present with more significant health crises or chronic ailments that may seem unresponsive to standard treatment strategies.

- Patients with connective tissue disorders will need to work on supporting the health of the ECM. The ECM contains immune cells called mast cells, which alert the body to injury or invasion by germs or

toxins. Ridding the body of toxins and infections and minimizing injury are ways to care for the ECM. Emotional stress and autonomic nervous system dysregulation can exacerbate inflammation in the ECM. Patients with connective tissue disorders, therefore, need a multi-systemic approach to management.

The Ehlers-Danlos syndromes (EDS) are described as a group of heritable, heterogenous connective tissue disorders. This means that different genetic variations are present with different classifications of EDS. EDS is not simply a diagnosis of joint hypermobility, rather it refers to connective tissue disorder that exists throughout the body, involving many different systems. Presentation with each patient will be determined by the type of genetic variation identified, along with how this gene expresses itself in the patient, which we will discuss in greater detail later in this chapter.

The human body consists of nervous, muscular, epithelial (skin), and connective tissue. Connective tissue composition is determined by the extracellular matrix, discussed later in this chapter. It can be found in the nervous and muscular tissue and adjacent to the epithelial tissue. As a function of its widespread reach, connective tissue plays many different roles within our bodies (Figure 2.1). For one, it helps package and compartmentalize areas of the body by providing support and/or protection. Additionally, it can bind and separate organs or other tissues. Connective tissue also plays a role in protection, defense, and repair. To do this work, it aids in scar tissue formation, inflammation, and defense against invading bacteria or other substances through some of its molecular components. It acts as insulation, storing energy as adipose tissue (fat). It also assists in the transportation of necessities throughout the body. For instance, blood is a connective tissue that delivers oxygen and nutrients throughout the body. Because it consists of blood cells surrounded by a fluid matrix called blood plasma, blood is considered a connective tissue. Fascia is a structuring connective tissue that creates a continuous system throughout the body, becoming a means of directing and transferring mechanical forces within the body. This means that dysfunctional connective tissue can lead to the transfer of inefficient forces that lead to physical imbalances and/or restrictions. Connective tissue is so ubiquitous within the body that some experts on the subject believe it to be the medium through which acupuncture treatment does its work; its remote actions may explain how needles inserted into the skin can affect organs from afar. Further, myofascial release experts purport that memory can be stored in the guarding patterns of the tissue, which may explain why some chronic, non-responsive fascial dysfunction can persist [41]. This all goes to show how multi-functional connective tissue is and how expansive its reach is within the human body.

Roles of Connective Tissues Throughout the Body
• Packaging and compartmentalizing • Protection, defense, and repair • Insulation • Transfer of mechanical forces throughout the body

Figure 2.1 Connective tissue assists with many different functions and roles within the human body. A connective tissue disorder can cause issues throughout the body, in any of these roles listed.

In fact, connective tissue is the most abundant tissue in our body, as it is found just about everywhere. It proliferates in fibrous tissues, fat, cartilage, bone, bone marrow, tendons, the wall of the gastrointestinal system, skin, and blood vessel walls. It also encases the brain and spinal column. So that it can perform this vast array of functions, connective tissue is made up of many different components — primarily elastin, collagen fibers, ground substance (gelatinous material that fills the spaces between fibers and cells), and immune cells. Those collagen fibers, with proteoglycans (protein) and glycosaminoglycans (polysaccharide compound), as well as other compounds, combine in different ratios to form the three-dimensional structure of the extracellular matrix. The distribution and ratio of each of these, within one type of connective tissue, will determine what it will look like (e.g., fibrous versus ligamentous). The resulting function of the connective tissue will be determined by the protein composition of the extracellular matrix (ECM).

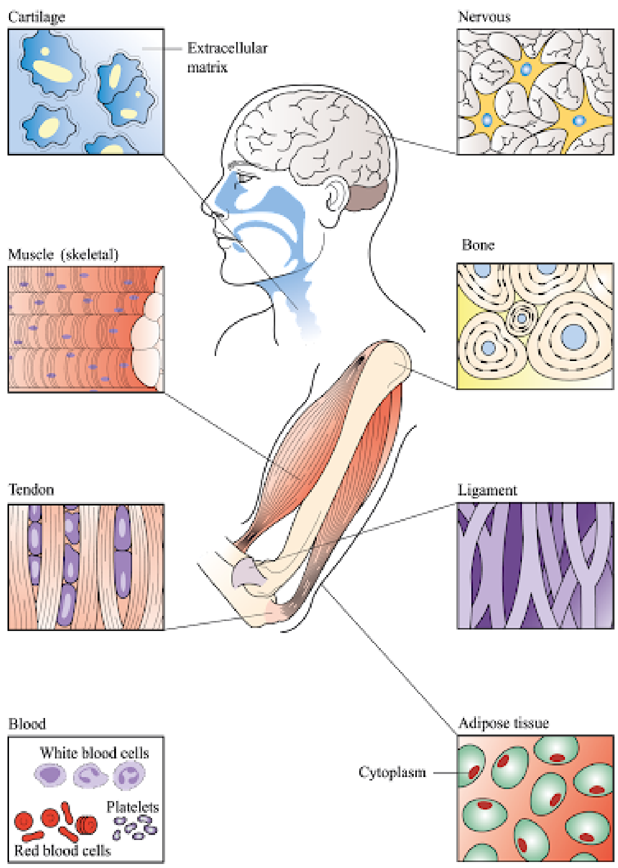

Figure 2.2 Connective tissue within the human body makes up cartilage, tendon, bone, adipose tissue, and ligaments. Connective tissue surrounds the blood vessel walls, muscles, and nerves, also influencing these systems.

Collagen

Collagen is the main structural component found in skin, bone, tendon, and cartilage. There are 28 different types of collagen within the human body, and each functions differently, depending on its composition and purpose. EDS is typically characterized by a dysfunction in collagen types I, III, and/or V, whether it is abnormal synthesis (creation) or organization of the collagen. There are some rare types that involve abnormalities in the proteoglycans and glycoproteins that form connective tissue and may affect the presentation of the structure.

Type I collagen is found mostly in bone, tendon, skin, blood vessels, the cornea, and organs. Type III collagen is a reticulate-supporting mesh, found in soft tissues like the liver, bone marrow, and tissues of the lymphatic system. Types I and III collagen are typically found alongside each other. Type V collagen is found in the placenta, cornea, skin, and tendons and also associates with Type I collagen throughout the body.

The following is a great reference from The Ehlers-Danlos Society website (figure 2.3) that groups the types of EDS into the specifics of collagen impairments. Collagen dysfunction can occur at any point in the process of making it. Depending on genetics, different connective tissue disorders will demonstrate collagen affected in different ways throughout the body. We replicated the table on the following page (figure 2.3) from the EDS Society website with permission.

Connective tissue will respond differently in a body with a disorder that creates faulty collagen, or other components of the extracellular matrix structure, compared with a body that makes normal collagen. For instance, in a body with healthy connective tissue, normal collagen makes the connective tissue strong. It will limit the stretching of the tissue, making it difficult to break. In this case, if connective tissue does break, it will repair and heal well. On the other hand, for a body with faulty collagen, as with EDS, the connective tissue the body produces will be weaker than normal. Although dysfunctional connective tissue can stretch easily, it breaks easily as well. Then, when it does break, the repair and healing process will also be affected. Unfortunately, this means that broken connective tissue will not heal as well as it would in a system that makes normal collagen.

Intake of collagen supplementation will not change the way the body synthesizes or organizes collagen within the body if this process is already altered in the patient (as seen in connective tissue disorders). However, those with additional cartilage issues (such as rheumatoid arthritis, tick borne illnesses, or other disorders that may additionally affect the cartilage) may find improvement with these supplements.

A Closer Look at the Cellular Level and its Implications

Examining the cellular level of the body helps

Pathogenetic mechanisms underlying the Ehlers-Danlos syndromes

There is an additional genetic classification structure of the EDS into groups according to similarities in the way the responsible genes affect the body.

Group A: Disorders of collagen primary structure and collagen processing, comprised of cEDS, vEDS, aEDS, dEDS, and cvEDS.

Group B: Disorders of collagen folding and collagen crosslinking, comprised of kEDS-PLOD1 and kEDSS-FKB14.

Group C: Disorders of structure and function of the myomatrix, comprised of clEDS and mEDS.

Group D: Disorders of glycosaminoglycan biosynthesis, comprised of spEDS-B4GALT7, spEDS-b3GALT6, mcEDS-CHST14, and mcEDS-DSE.

Group E: Defects in complement pathway, comprised of pEDS.

Group F: Disorders of intracellular processes, comprised of spEDS-SLC39A13 and BCS.

Group G: Unresolved forms of EDS, comprised of hEDS.

Conditions no longer included in the EDS spectrum are occipital horn syndrome, fibronectin-deficient (EDS X), familial articular hypermobility (EDS XI), X-linked EDS with muscle hematoma (EDS V), and filamin A related EDS with periventricular nodular heterotopia.

Figure 2.3 Ehlers Danlos syndromes divided into pathogenetic mechanisms of the connective tissue. Table used with permission from The Ehlers-Danlos Society: https://www.ehlers-danlos.com/eds-types/

shed some light on why certain patients experience more severe health crises than others. In general, when structural components of the ECM are compromised, as with a connective tissue disorder, then the 3-D structure, supported by the ECM, will also be compromised and potentially incapable of efficient functioning. As reported in Gensemer et al. (2021), "modification of the ECM likely plays a major role in impairing the mechanical stability of the affected tissues in EDS patients" [11].

What is the ECM?

The ECM is the three-dimensional area surrounding a cell that acts as a filtering system between the cell and its surrounding environment. It is defined as a functional unit consisting of the capillary bed, connective tissue cells, and the autonomic nerve endings [30]. Many compounds make up the ECM, including: electrolytes, glycosaminoglycans, polysaccharides, collagen, and other proteins. The function of connective tissue depends on the biochemical properties of the ECM, as is determined based on the ECM protein composition ratio. In dense connective tissue, collagen is the main structural stabilizing component of the ECM; whereas, proteoglycans stabilize loose connective tissue. Depending on the density of the connective tissue, one of those components will provide tensile strength, regulate cell adhesion (how neighboring cells interact with each other), support chemotaxis (the cell's reaction to chemical stimulus), encourage cell migration (movement to areas it is needed), as well as to facilitate tissue development [18].

The ECM is important to overall health regulation because many regulatory functions and activities happen at this level. As such, it is crucial to perceive the patient at the cellular level in order to understand the basics of how their health is impacted at this level. The following sections provide a brief overview of the potential and theoretical involvement of the ECM in connective tissue disorders like HSD/EDS. If the information regarding the ECM resonates with any patient readers, we recommend that they seek out the services of a specialized provider, well-versed in how the ECM functions. This will be an individual specialization for a medical provider, not determined by the kind of professional you see.