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Viscoelastic Properties of the Human Dermis and Other Connective Tissues and Its Relevance to Tissue Aging and Aging–Related Disease

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1. Introduction

Skin is the largest organ in humans and protects the body from environmental factors. The dermis is a layer that acts to protect the body from external physical force. Viscoelasticity is essential to facilitate the physical function of the skin. However, the clinical-biological-physical relevance of dermal connective tissue has not been fully investigated. In this chapter, we review past studies in this vast field and attempt to elucidate the combined clinical-biological-physical relevance of dermal connective tissue. In addition, we discuss Tarumi disease, which is characterized by impaired viscoelasticity and stiffness in connective tissues.

2. Extracellular matrices contribute to the viscoelastic properties of connective tissues including the dermis

The viscoelastic properties of human tissues are principally governed by the nature of the extracellular matrix (ECM). The ECM comprises secreted proteins that are deposited into the extracellular space. Although cell-ECM interaction and growth factor-ECM interactions have recently been investigated, the ECM represents the fundamental architecture of tissue. Some ECM proteins supply the connective tissues with hydration and resiliency through their characteristic molecular properties and assembly. ECM proteins such as collagen, proteoglycans, and glycoproteins are classified by their biochemical properties rather than their physical properties. Numerous ECM proteins are currently known and have been well characterized biologically. However, the contribution of each ECM protein to the viscoelastic properties of tissues has not been fully investigated due to the lack of a proper experimental system. Therefore, the contribution of each ECM protein to viscoelasticity in human tissue should be determined based on biological, physical, and clinical studies.

3. Connective tissue elements in the dermis: Collagen fiber, elastic fiber, and ground substance

As the dermis is the layer that protects the body from physical stress, understanding the nature of dermal connective tissues is vital. In this section, 3 components of connective tissues and the ECM are briefly introduced. ECM molecules are produced primarily by fibroblast cells.

Collagen fibers are major elements of the dermis and collagens are the most abundant protein in the human body; the dermis alone is composed of approximately 75% collagen proteins in dry weight. Twenty-eight collagen species have presently been identified. It has been reported that skin contains collagen types I, III, IV-VII, XIII, and XIV, with the major collagen in the dermis being type I collagen. Collagens that associate with the type I collagen fiber are classified as FACIT collagens and can provide additional mechanical properties to tissues. Collagens are characterized by repeated glycine-X-Y sequences and form triple-helical structures that are extensively modified after their secretion into the extracellular space. In immature tissues, such as those found in wound healing and fibrosis, type III collagen is expressed; however, it is not yet strong enough to support mature connective tissues. As the wound matures, type I collagen becomes dominant. Heterotypic type I and type III collagen fibrils are present in the dermis. Type VI collagen individually forms a unique filament called a microfilament (1,2).

Elastic fiber comprises elastin and microfibrils. As the dermis has to be stretched to adapt to the movement of body parts, elasticity is a critical property of the dermis. Elastin—a unique molecule that stretches and shrinks—is secreted as tropoelastin (the soluble precursor of mature elastin) and is subsequently processed and cross-linked within the extracellular space. Cross-linking by lysyl oxidase and desmosine formation is a crucial step for the stabilization of elastin within tissues. Another element in elastic fibers is fibrillin-microfibril. Microfibrils are fibrous elements that are 10 nm in width and are comprised mainly of fibrillins. Fibrillin is a large glycoprotein that is rich in cysteine residues and homotypically assembles into a microfibril in a well-regulated manner (3, 4). Fibrillins align in a parallel manner, from head to tail, in a staggered fashion within extracellular microfibrils (5). Other ECM molecules, including microfibril-associated glycoproteins (MAGPs), latent TGF-beta binding proteins (LTBPs), type XVI collagen, emilin, and versican, can associate with microfibrils through their binding affinity with fibrillins. Fibulins are yet another elastic fiber component, which can bridge elastin and microfibrils by their binding properties. Interestingly, fibulin-5 knock-out mice exhibit skin looseness (6, 7), indicating that this molecule may be essential for the development of elastic tissue.

Thick elastic fiber distributes horizontally in the reticular dermis, whereas thinner elastic fiber, including elaunin and oxytalan fibers, are seen to distribute in the papillary dermis. Oxytalan fibers are formed by bundled microfibrils without amorphous elastin. The staining of fibrillin in the skin shows horizontal distribution in the reticular dermis and vertical orientation in the papillary dermis (Figure 1). This complex elastic fiber meshwork confers the dermis with the ideal viscoelasticity to effectively protect the human body.

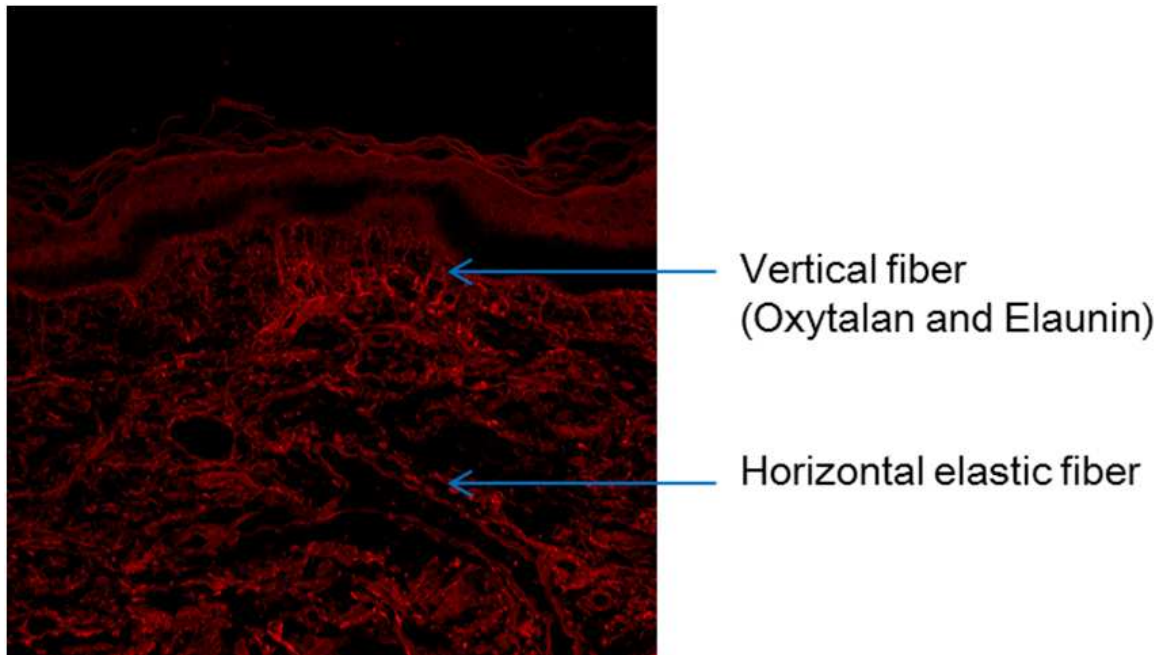


Figure 1. Immunohistochemical staining of fibrillin-1 in the human dermis. The distinct alignment of elastic fiber elements differs between the layers of the dermis

Proteoglycans are glycosaminoglycans (GAGs) that are covalently linked to a core protein. GAGs can be chondroitin/dermatan sulfate, heparan sulfate, heparin, and hyaluronan. GAGs hold a large amount of water within connective tissue, whereas free water in connective tissue is observed as edema. In particular, hyaluronan (HA) has a high affinity to water through its charge and, in general, is a high molecular weight linear GAG that distributes ubiquitously in connective tissue. Proteoglycans are major components of ground substance and are occasionally associated with fiber components in the dermis. Therefore, GAG is essential for maintaining the tissue viscosity of dermal connective tissue. In dermal connective tissues, decorin and versican are the major proteoglycans (8). Decorin is a small dermatan sulfate proteoglycan that binds to type I collagen. In the dermis, decorin is abundant in the papillary and the reticular dermis. Scott et al. have proposed that, through their charge, GAG chains of decorin can play a role in the viscoelastic property of connective tissue (9, 10). These models highlight the importance of GAG chains to the viscoelastic properties of connective tissues.

The supramolecular organization of the ECM in the dermis has been investigated using biochemical, biophysical, and ultrastructural methods. Connective tissues are not composed of a simple mixture of ECM molecules; therefore, the manner in which the ECM molecules assemble into fibrous components should be further investigated (11). In the dermis, each ECM molecule assembles into either elastic fibrous elements or ground substance. This can be observed in the electron micrograph of dermal connective tissue shown in Figure 2. Collagen and elastic fiber distribute distinctly, whereas the “empty space” is believed to be filled by ground substance. Thus, collagen and elastic fiber is embedded within ground substance, which itself is comprised of proteoglycans and hyaluronan.

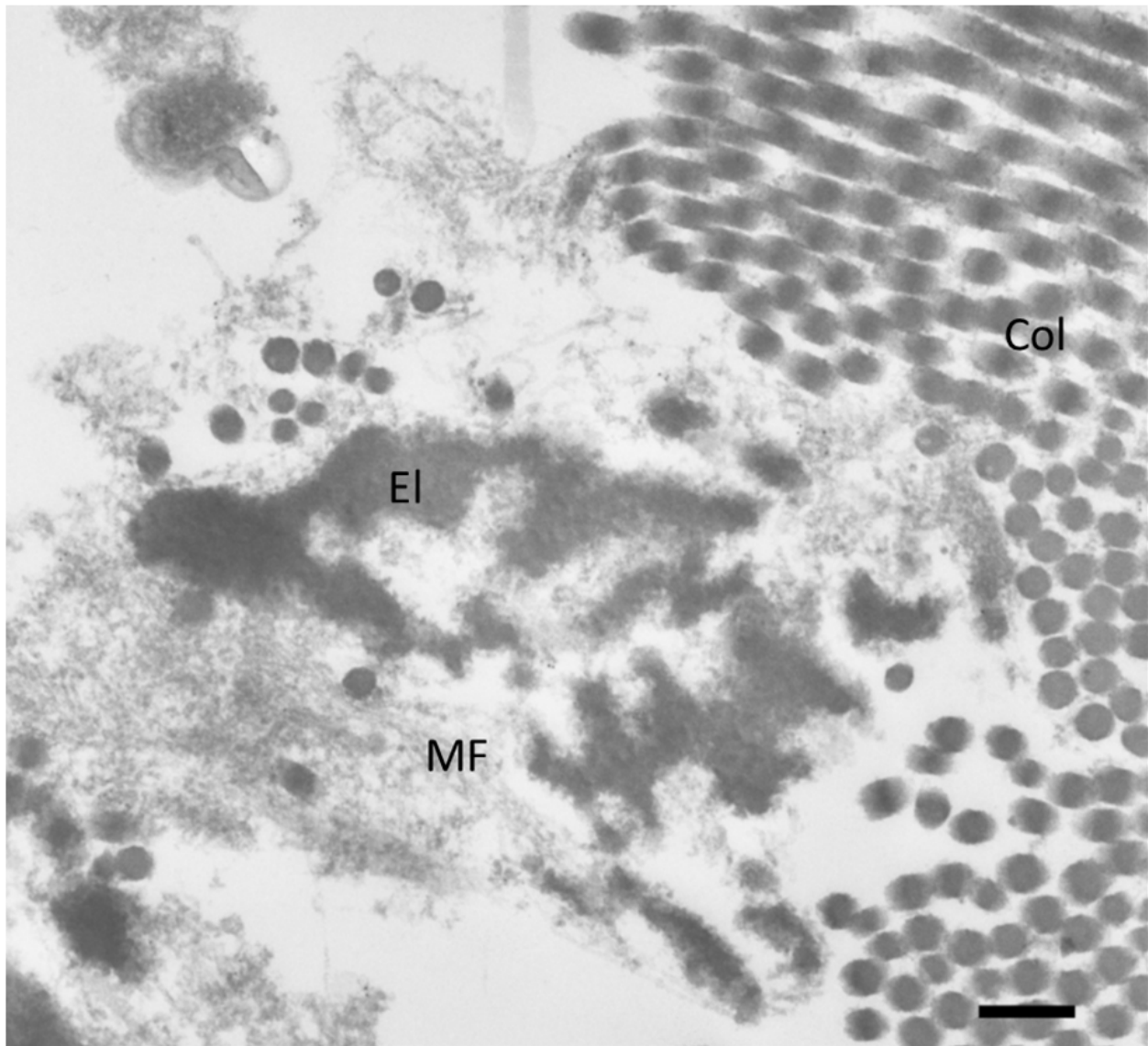


Figure 2. Electron microscopic image of dermal connective tissues. Col: collagen fiber, El: elastin core, MF: microfibrils (Bar = 200 nm)

4. Versican is a chondroitin sulfate proteoglycan and is critical for dermal viscoelasticity

Among the ECM molecules in the dermis, versican appears to be the most important molecule for tissue viscoelasticity. Versican (also called PG-M) is a large chondroitin sulfate proteoglycan that was originally characterized in a mesenchymal condensation in chick limb bud (12). Versican binds to hyaluronan via its amino-terminal G1 domain and to fibrillin-1, fibulin-1 and fibulin-2 via its carboxyl terminal G3 domain. The distribution of versican is similar to that of elastic fiber in the dermis and in other tissues (13, 14) and is immunolocalized to microfibrils through its binding affinity to fibrillin-1 (15) as observed in Figure 3.

Thus, versican plays critical roles in the viscoelastic properties of skin. Versican 1) connects with elastic microfibrils by binding to fibrillin via its G3 domain; 2) has chondroitin sulfate

chains that hold a large amount of water within the ECM space; and 3) binds to HA, which holds a large quantity of water. Figure 4 shows the proposed structural model of the elastic-hydrated matrix in the dermis. Furthermore, the fibrillin-versican-hyaluronan network is also observed in the ciliary body (16).

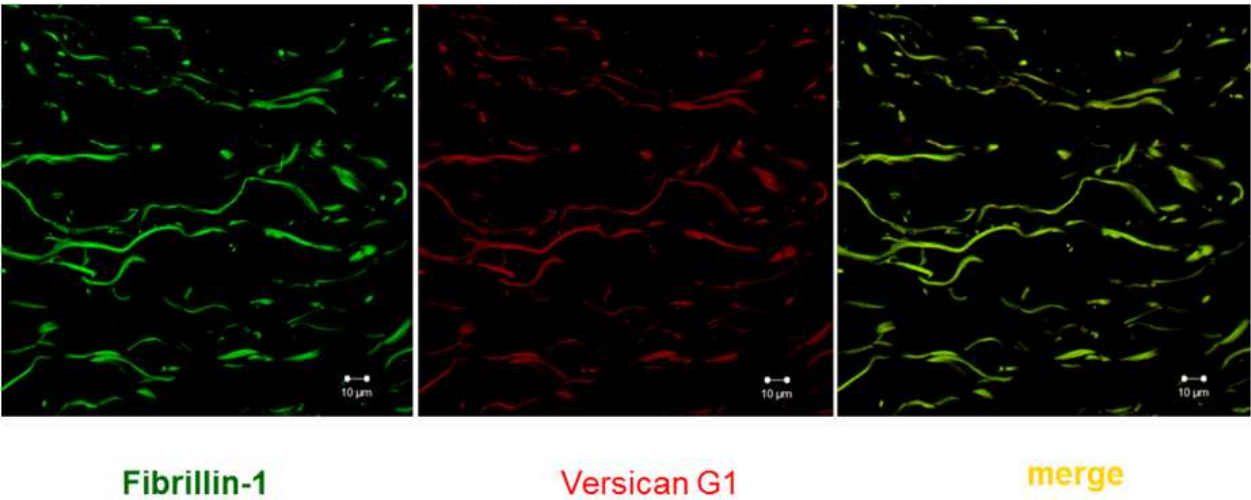


Figure 3. Versican co-localizes with fibrillin-1 in the dermis. Immunofluorescent staining using specific antibodies against versican and fibrillin-1 show co-localization.

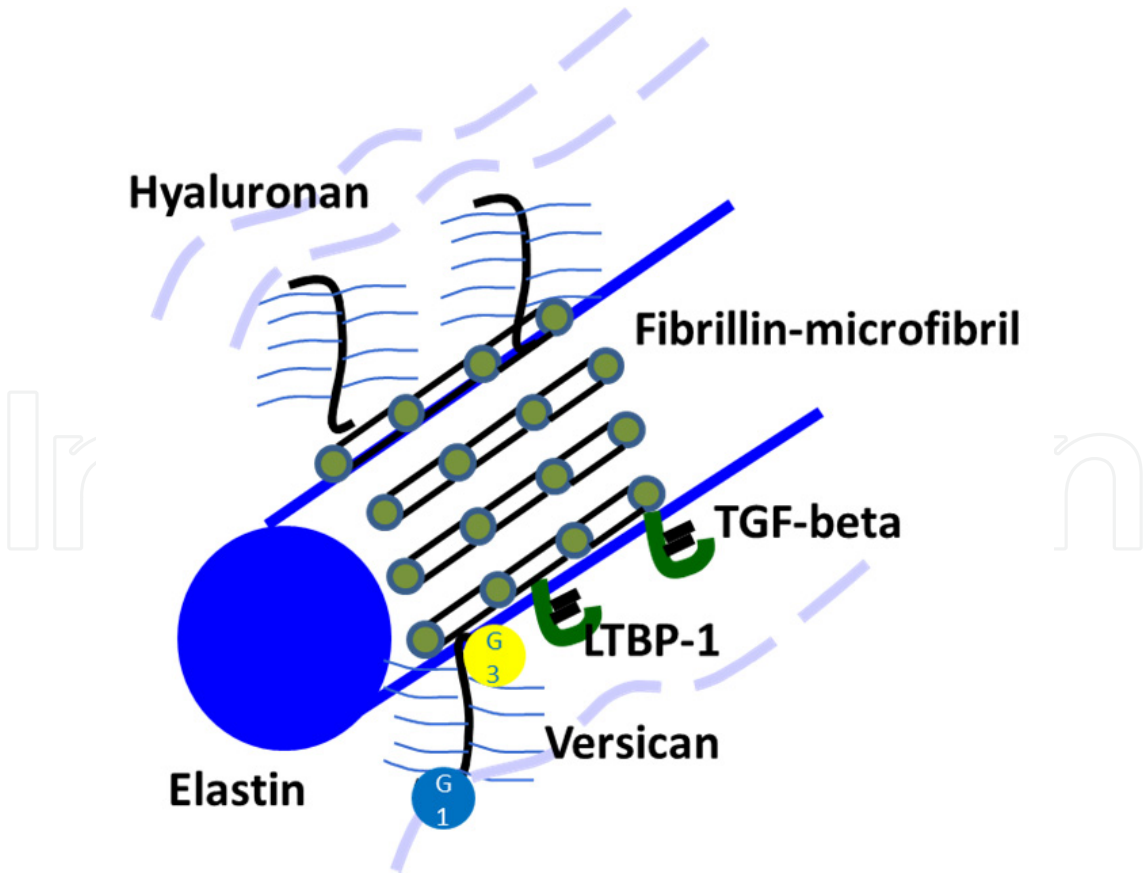


Figure 4. Schematic presentation of the dermal viscoelastic network linked by versican. Versican links elastic fibers to ground substance.

5. Biophysical examination of the skin and subcutaneous tissues

The fundamental role of human skin is to protect the body from invasion by external factors. Biological and chemical invasions of the body could be prevented by the skin, which include circulating cells of the innate immune system. Furthermore, protection from physical invasions—such as mechanical force and thermo injuries—are also important to maintain the homeostasis of the human body.

Skin consists of 3 layers, which include the epidermis, dermis, and subcutaneous tissue. Skin covers most of the body's surface, except for some "holes such as oral cavity". Thus, the physical barrier that skin provides is crucial to protect the human musculoskeletal system and internal organs. The physical properties of skin have been measured using several devices (17). In this study, the authors measured the mechanical properties of the skin by dynamic indentation. This study noted that the measurement of these mechanical properties by indentation is not well correlated with that by suction. (17). Furthermore, they also reported the aging-associated alteration of mechanical properties of the skin (18). The Cutometer™ has been used to measure the viscoelasticity of skin. Additionally, we have recently established a novel method to measure the viscoelasticity of skin using a rheometer (AR instrument, AR 550) (Figure 5).

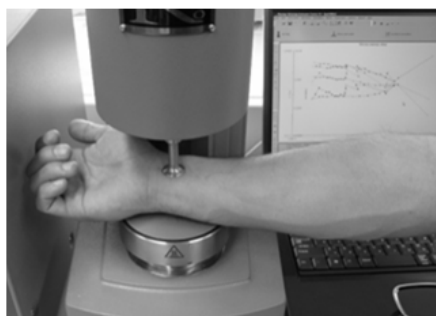


Figure 5. A rheometer can be used to determine the viscoelasticity of skin.

Using this method, skin is treated as a complex of different materials. The skin surface at the bottom of an appendage is immobilized so that deformity is only obtained by the external force generated from the upper probe. From the results shown in Figure 6, viscoelasticity of skin (and subcutaneous tissues) was estimated to be approximately 30 kPa. This data was not influenced by muscle contraction, thus indicating that the origin of the physical properties of skin could be the fascia (19).

Next, we developed a physical model for pressure ulcers and mechanical force around the ulcer was measured using our new device, real time skin strain monitor (RTSSM). A pressure ulcer is characterized as a skin and soft tissue injury caused by an external force on a bony prominence. However, it is not clear how a pressure ulcer is strained by external force. Previous studies have reported the similarity in strain properties of human soft tissue and industrial buffer materials. Therefore, we utilized a cell sponge as a testing material for its physically similar attributes to soft tissues. As shown in Figure 7, a physical model for pressure ulcers was developed. Strain gauge probes were stitched around the pressure ulcer model as indicated.

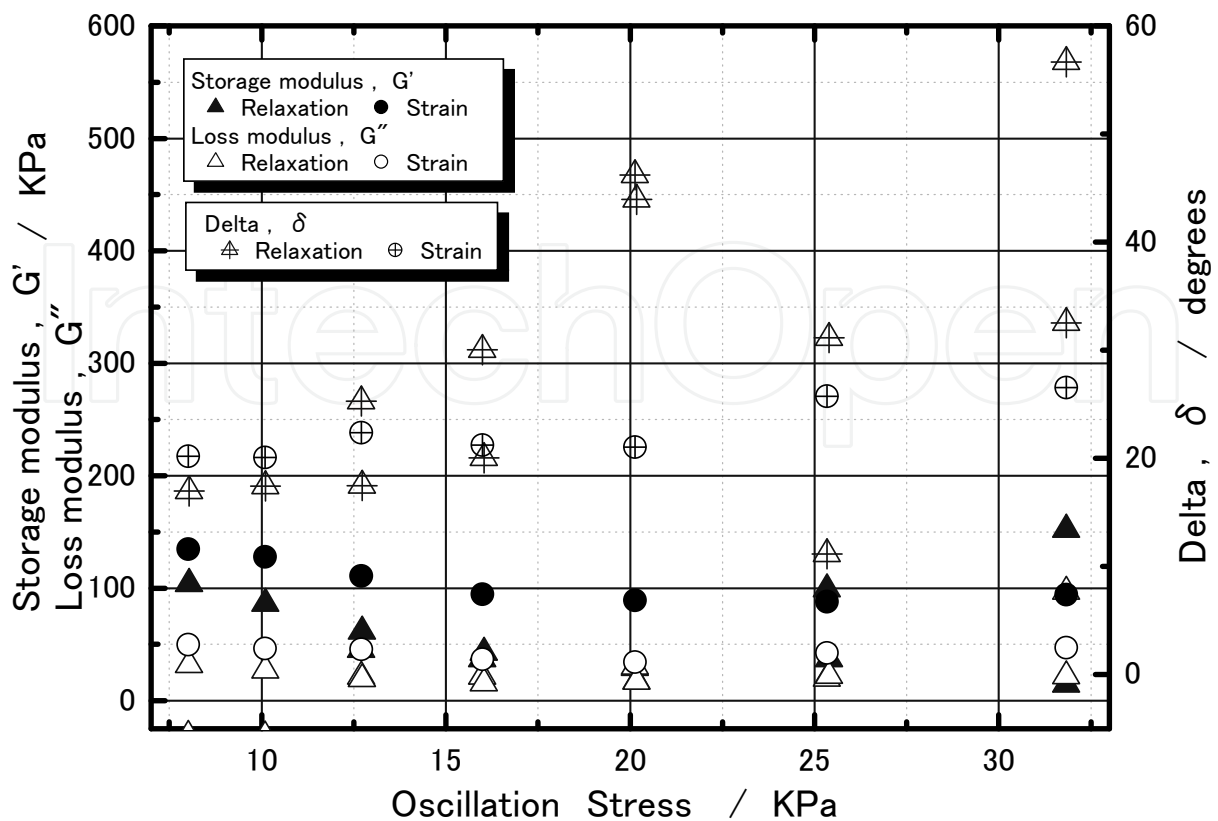


Figure 6. Viscoelasticity measurement by muscle contraction.

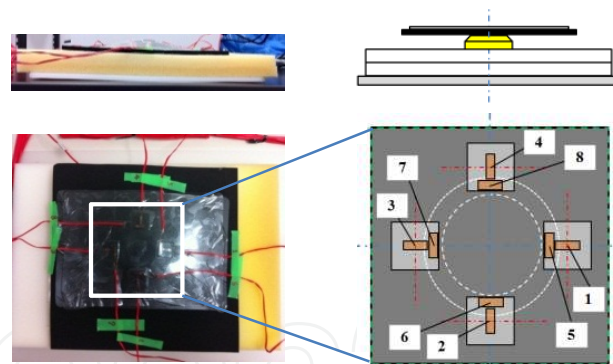


Figure 7. The composition of a pressure ulcer model and the positions of strain gauge probes. The physical model for the pressure ulcer is made of sponges; the probes are placed around the hole mimicking pressure ulcer.

Figure 8 shows the data observed from RTSSM when a tensile load is applied toward the channel 2–4 direction. From the results, it can be observed that this method is able to measure the strain force during the loaded state (0–0.3 seconds) and the relaxed state (after 0.3 seconds).

We further examined our model by testing the strain force around a pressure ulcer in a patient. This study was approved by the ethics committee of our institution and performed following written informed consent was obtained from the patients. As shown in Figure 9,

the probe was adhered onto the dressing and the strained force was measured in the bedridden patients.

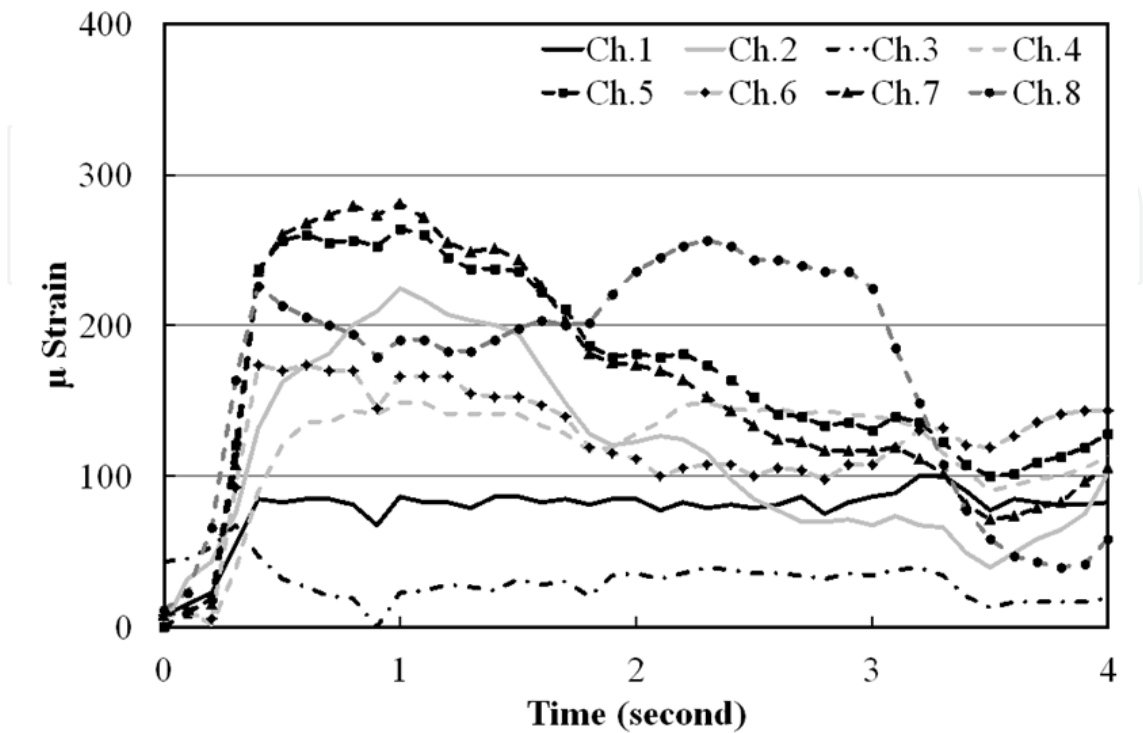


Figure 8. RTSSM measured by the strain distribution of a pressure ulcer model. The loading force is increased by 100 μ strain/s from the initial load at 50 μ strain/s and a maximum force of 250 μ strain/s is maintained.

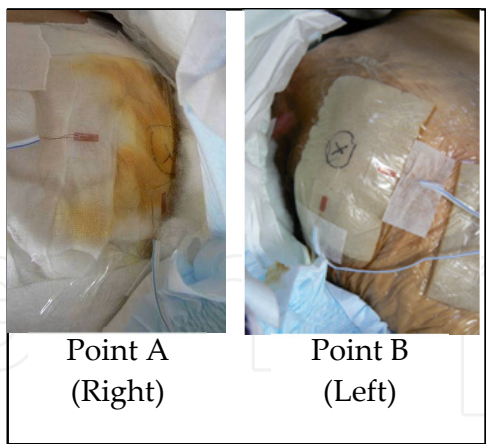


Figure 9. Measurement of strain force around pressure ulcers.

It has been noted that the head lifting position of the patient can occasionally worsen a pressure ulcer. Therefore, the manner in which positioning changes influence a pressure ulcer is an important issue for the care of a patient. To address this issue, we measured strain forces around the pressure ulcer during positioning changes. Measurement using RTSSM indicates that a positioning change can generate a strain force around the wound (Figure 10).

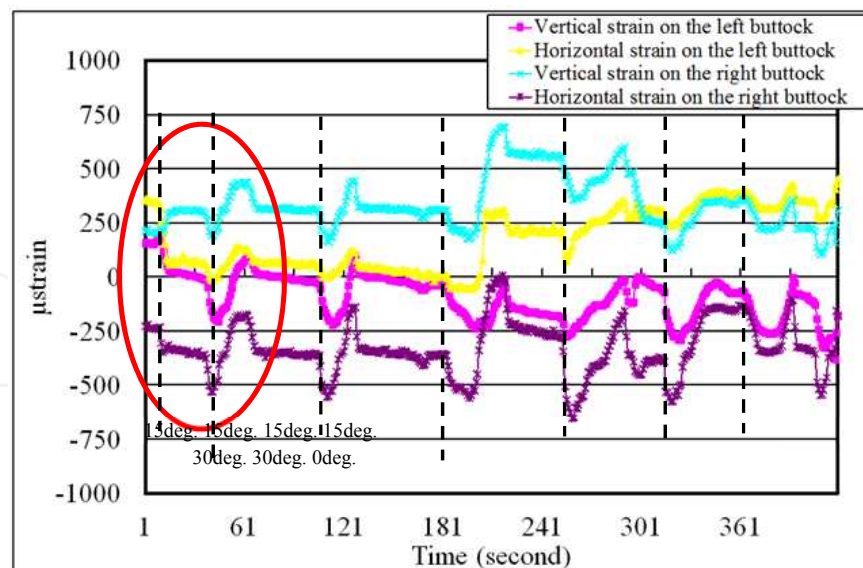


Figure 10. Changes in strain force at the buttocks are dependent on a positional change in head lifting.

Using the RTSSM, we next determined the direction of force by coordinating data from several probes. To this end, multiple probes can be adhered around the wound (Figure 11) and the measured force can be generated. In this case, it was reasoned that the different vectors, representing the strain force between the right and left sides, were generated due to the contracture of the right leg. Thus, the data obtained can be used to determine the positioning change that is ideal in the care of the patient with a pressure ulcer (20).

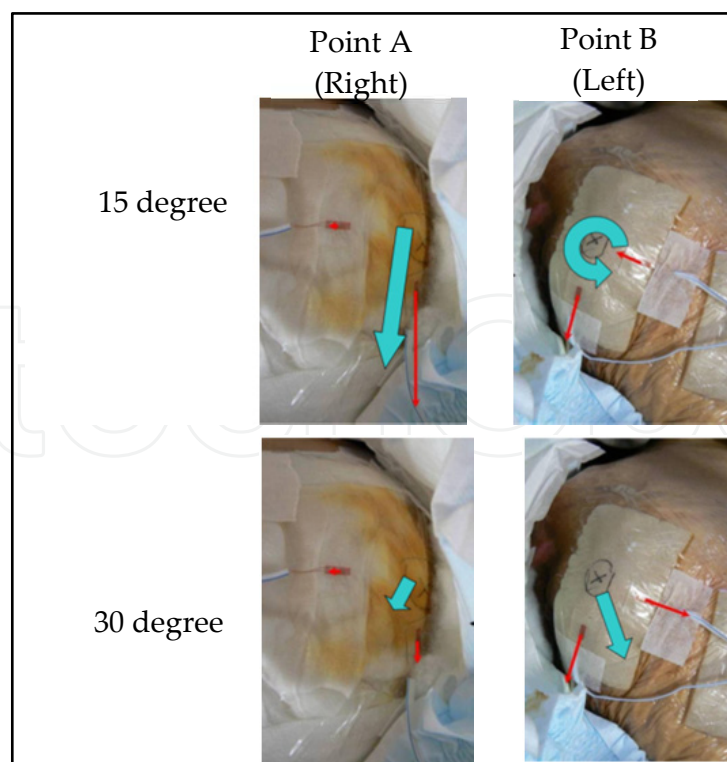


Figure 11. Positioning changes generate strain force on a pressure ulcer toward a specific direction. When the position of head is lifted at the indicated degree (15 or 30) a strain force is promptly changed.

6. Diseases caused by impaired viscoelastic properties of connective tissues

We discuss aging-associated diseases that result in impaired physical properties of connective tissues based on a review of genetic diseases that cause impairment in the physical properties of connective tissues.

Marfan syndrome (MFS) is a relatively common genetic connective tissue disease. MFS is an autosomal dominant connective tissue disease that affects the aorta, lungs, ciliary zonule, muscles, and other organs. However, most phenotypes appear only in the later stages of life. The primary cause of MFS appears to be due to mutations in the microfibrillar molecule fibrillin-1, although some phenotypes observed in various organs are believed to develop from the dysregulation of TGF-beta. One explanation for the genotype-phenotype correlation is due to the aberrant activation of TGF-beta stored within microfibrils through the binding between fibrillin-1 and LTBP (21) (Figure 4). Recent studies have highlighted the importance of proper modulation of non-canonical TGF-beta signaling (22). The role of versican in MFS is currently unknown. Interestingly, the tissue phenotype resulting from MFS shows similarities to that of aging. For instance, aneurysm, emphysema, hernia, and muscle atrophy are all common features of MFS patients and also of elderly patients. However, the correlation between MFS and aging connective tissue phenotypes is currently unknown. MFS appears to be a model for impaired viscoelasticity of human tissues, which is discussed in the following section.

7. Aging-dependent changes of versican in the dermal connective tissues

The dermis changes prominently with age; for example, the thickness of the dermis becomes thin and wrinkles appear. Biochemical collagen content and histological density of collagen fiber is reduced (23). We have shown that versican is a key molecule for viscoelasticity of the dermis. The amount of versican extracted from the dermis decreases with age and its GAG composition is also altered (24, 25). Therefore, as described above, we hypothesize that loss or reduction of versican, or in the HA binding ability of versican, may lead to impaired viscoelasticity of the dermis. Versican is heavily accumulated within solar elastosis, which is a hallmark of photo-aged skin and where elastic fiber components, including elastin and fibrillin-1, have accumulated (26). Clinically, photo-aged skin is not viscoelastic and shows deep wrinkles, as observed in Figure 12.

Using recombinant versican G1 proteins and specific antibodies, we have indicated that a loss in the HA binding affinity of versican is characteristically observed in the region of solar elastosis (27). Versican specifically loses its HA binding domain (6084) in solar elastosis, whereas the carboxyl terminal domain (2B1) remains present. Therefore, the HA binding ability of elastic fibers is lost and microfibrils in solar elastosis are unable to bind to HA (Figure 13). Therefore, loss of the HA binding region of versican disrupts the fibrillin-versican-hyaluronan (Fi-Ver-Hy) network in the dermis.

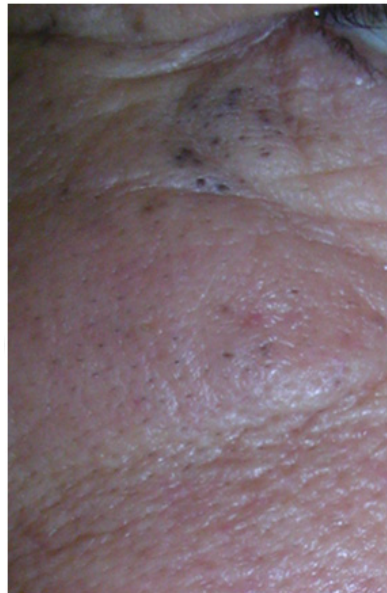


Figure 12. Clinical appearance of photo-aged skin. Deep wrinkles and comedo (black dots) are observed.

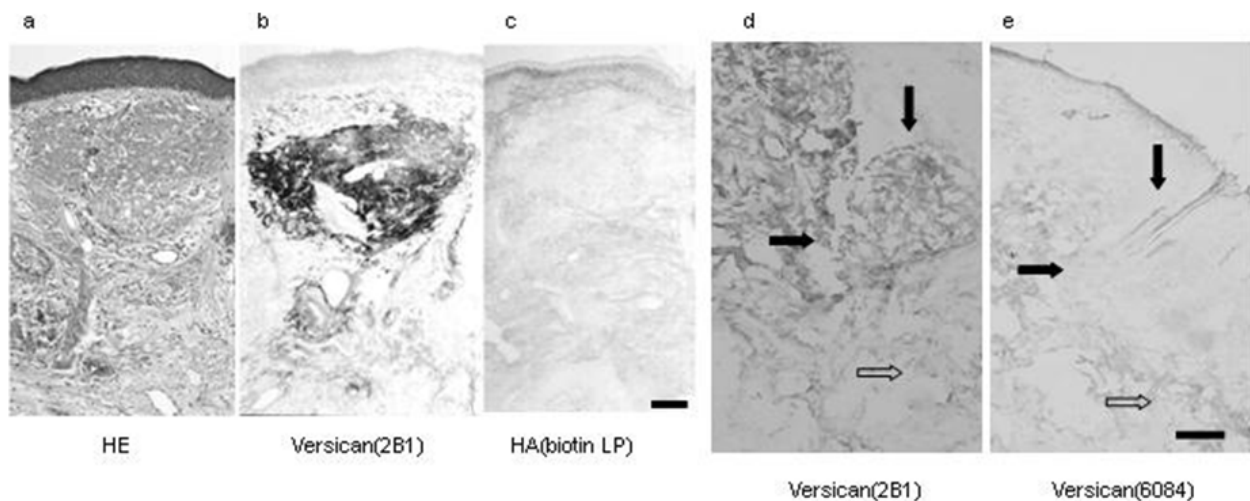


Figure 13. Histochemical results of solar elastosis. Versican is detected by its anti-fibrillin binding region (2B1) or its anti-HA binding region (6084). HA is detected using a biotin-conjugated link protein (biotin LP).

8. Tarumi disease

Based on the physical properties of skin and other connective tissues, we propose “Tarumi disease” as an aging-associated, connective tissue loosening disease. Tarumi diseases are preferentially found in the elderly population, with some exceptions. Tarumi is a Japanese word that represents tissue loosening. Aging-associated loosening of connective tissue is a major pathogenesis for emphysema, aneurysm, skin wrinkles, pelvic organ, and hernias. The Tarumi diseases that we are proposing are listed in the table below (Table 1). In 2001, an interesting association between pseudoexfoliation syndrome and abdominal aortic aneurysm was reported (28). However, it should be noted that this report has not been supported by the subsequent studies on the prevalence of these conditions.

Common pathogenesis among each Tarumi disease is currently unclear. Smoking is considered to be a precipitating factor in the common pathogenesis of aortic aneurysm and chronic obstructive pulmonary disease (COPD) (29, 30). However, other factors should be investigated for the Tarumi diseases. Tarumi disease may provide a novel perspective of tissue aging in geriatrics.

Therefore, studying Tarumi disease may be a useful step toward understanding common pathogenesis among these diseases. Future directions in Tarumi disease research require pathological, biochemical, and physical studies. Methods presented in this chapter may evaluate the looseness of tissues. Furthermore, surgical intervention using a tissue filler may be a useful method to improve these diseases. Finally, the phenotypical relationship between MFS and Tarumi disease may lead to understanding their common pathogenesis.

Organ	Proposed diseases
Aorta	Aortic aneurysm
Lung	Chronic obstructive pulmonary disease
Pelvis	Pelvis organ prolapse
Vein	Varicose vein
Skin	Wrinkles, Pressure ulcer
Abdomen	Hernia
Esophagus	Esophageal hiatal hernia

Table 1. Proposed Tarumi diseases.

9. Conclusion

Viscoelastic properties of the skin can be measured by various methods and are dependent on the connective tissue architecture formed by ECM molecules. In order to measure the actual viscoelasticity of the skin, we have developed a novel device that can monitor the external forces on the skin in real time. The device can be used for treatment and prevention of pressure ulcers that are affected by viscoelasticity and external force. Among the ECM molecules, versican—a chondroitin sulfate proteoglycan—is an important ECM molecule for viscoelasticity because it constitutes the fibrillin-versican-hyaluronan network. In human pathogenic conditions such as solar elastosis, loss of viscoelastic properties of the dermis is found to occur because of the loss of hyaluronan-binding versican. Marfan syndrome—a genetic connective tissue disease—is also characterized by loss of viscoelasticity in elastic tissues, such as those in the aorta. Finally, aging-associated loss of viscoelasticity and stiffness of connective tissue are proposed to be the common pathogenesis of Tarumi disease.

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