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Research Article

Connective Tissue Breakdown: Remodeling, Repair, and Prevention Using an Inclusive Method of Treatment

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Abstract

Because new methods that prevent connective tissue-deteriorating processes are desirable to delay aging, stave off disease, and improve wound healing, the study of the Extracellular Matrix (ECM) is a rapidly expanding field. Countless epidemiological studies, research, and experiments have demonstrated the pathophysiology of connective tissue, including the complex interactions that occur at the cellular level, which involve the fibroblasts, inflammation, matrix metalloproteinases, protein synthesis and cell proliferation. While much is known regarding the factors that contribute to connective tissue weakening, a systematic or inclusive approach for remodeling, repair, and prevention of damage to the body's framework or support structure has been elusive, until now. This article will briefly review the current literature and pathophysiology of connective tissue. Additionally, it will focus on a patient-specific, inclusive approach of treatment, based on the cellular water principle theory, which aims to systemically fortify, restore, and remodel cells and connective tissue, Increase Intracellular Water (ICW), reduce inflammation and boost collagen formation. A discussion of the new method and its value in improving patient health and wound healing is also included.

Keywords: Collagen; Combination therapy; Connective tissue; Cultural stress; Cultural stress anxiety Syndrome; Extracellular Matrix (ECM); Nutraceuticals; Nutrition; Senescence; Skin aging; Stress

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Introduction

Research on aging including therapies for external, internal, and emotional concerns will continue to expand to accommodate for the demands of baby boomers who are seeking to stay young as old as possible. The youngest baby boomers turned 55 this year and while many of them are looking forward to retirement, you can be assured that none are looking forward to aging. With intrinsic and extrinsic aging, certain deteriorations may occur giving rise to disorders and illnesses such as arteriosclerosis and cardiovascular disease, ocular disorders, skin laxity, cellulite, arthritis, and joint problems, to name a few. These conditions have one thing in common: connective tissue. Because connective tissue deterioration in the body can have far-reaching, systemic effects, much research has been devoted to decoding its mechanisms.

Studies on connective tissue have produced valuable data, which have stimulated the creation of treatments for preventive and rejuvenative health care. Treatments have focused on external therapies such as skin care and esthetic medicine; others concentrate on internal solutions, delving into nutrition, medication, diets, and supplements; lastly, a small number of programs have examined patient psyche to find methods of reducing emotional stress and anxiety. While these treatments on their own may produce some results, it is plausible that even greater results can be achieved if used together in an inclusive model of care. In fact, some in the medical community are already using comprehensive systems or multidisciplinary approaches including alternative interventions to address systemic health and are seeing real value in offering inclusive health care, citing that individual protocols lack synergy or continuity of care, topically, internally and emotionally. Such is the case in our office, as well-documented therapies and agents are combined in an all-encompassing, multidisciplinary approach. In this way, we feel that inclusive health care may be the most appropriate strategy for cell and connective tissue remodeling, repair and prevention of future damage.

Connective tissues are the structural components of the body and are found in the ECM. These tissues provide the systemic scaffolding or framework the body needs to literally hold it together, joining layers of muscles and organs, providing the vascular highways that deliver nutrients to every part of the body. There are three types of connective tissue: loose, fibrous and specialized. Loose connective tissue consists of collagenous, elastic, and reticular fibers, which are responsible for holding organs, epithelial tissue and underlying layers together. Fibrous tissue is found in tendons and ligaments and features dense collagen formations. Specialized tissue includes bone, adipose tissue, cartilage and blood.

Deterioration of these tissues occurs because of intrinsic and extrinsic aging. Specifically, human skin becomes fragile because of fragmentation and the loss of type I collagen fibrils, which make the connective tissues strong and resilient. Fragmentation promotes oxidation and in turn, elevates Matrix Metalloproteinases-1 (MMP-1) levels. One study demonstrates that dermal fibroblasts express increased levels of collagen-degrading MMP-1 in aged (>80 years old)

compared with young (21 to 30 years old) human skin in vivo, additionally, MMP regulators also become elevated [1]. As a result of these findings and others, it is now believed that aging is not just relegated to cells, rather it includes the ECM and it is plausible that the connective tissue microenvironment may play a vital role in the biology of not only cutaneous aging but also systemic disease.

Pathophysiology

Many connective tissue diseases feature similar and overlapping routes of damage, which may be the result of an immune system disorder and/or the weakening of collagen. Connective tissue deterioration can occur because of oxidative stress [2] and environmental factors, with the risk increasing with detrimental lifestyle choices including poor diet and smoking [3,4]. Connective tissue damage may also occur because of physical injuries such as those that may be experienced during sports activities. Some diseases are inherited such as Marfan syndrome and Ehlers-Danlos syndrome, and others have no known cause: systemic lupus erythematosus, rheumatoid arthritis, scleroderma, polymyositis and dermatomyositis [5]. And, there is growing evidence that chronic psychological stress can have adverse effects on connective tissue [6].

For the sake of organization, a patient's degree and risk of connective tissue damage can be categorized in three ways: external, internal and emotional. For example, in patients with poor connective tissue function, externally, the cutaneous layer may exhibit laxity, deep wrinkles and in places, cellulite may be present. Internally, there may be inflammatory disorders that involve the vascular system, joints, tendons, ligaments, blood and hormones. Emotionally, incessant and unabated stress (also identified as Cultural Stress [7]) has been well documented to cause hormonal imbalance, telomere shortening, and sleeplessness, which can affect healing, cell replication and immunity [8,9]. In specific, sleeplessness is complexly associated with depression, diabetes, dementia, heart problems, chronic pain and stroke [10] -all of which can have specific influence on connective tissue remodeling, repair and damage prevention.

Connective tissue: Development, repair and remodeling

Connective tissue is an all-encompassing term the diverse, fibrous and semisolid material that binds muscles and organs in place, as well as connects one organ to another [11]. Comprised of ground substance, fibers, and cells, connective tissue includes loose, dense, and specialized connective tissue that is classified as the body's matrix: semisolid matter made of blood vessels, nerves, collagen and elastin fibers, adipose, cartilage, bone and blood, and internal layers of skin [12]. Connective tissue houses the bulk of the body's water through hyaluronan, or hyaluronic acid, a hydrophilic Glycosaminoglycan (GAG) that is a dominant component of the extracellular matrix. Hyaluronic acid can attract and hold up to one thousand times its weight in water and despite what is considered a simple chemical composition, and plays a major role in human function including development and repair [13].

As we age, cellular and connective tissue water loss occurs in response to both intrinsic and extrinsic factors. When dehydrated, cells may not function properly or replicate normally. The most visible indicator is skin wrinkle formation that is partially caused by subcutaneous water loss that happens as we age [14]. Connective tissue that has experienced water loss may become fragile, as collagen fibers grow rigid and elastic fibers lengthen and become lax. Free-radical damage, inflammation, and other factors may stimulate repair, but repair processes may be unpredictable, insufficient, in excess and in disorder. As a result, connective tissues, overall, may lose their resiliency and resistance to compression and tension, further increasing the risk of damage. Tissue remodeling is a repair response to damage. Connective tissue repair involves the immune system because damage or injury stimulates the fibroblasts and synovial cells to release pro-inflammatory cytokines, prostaglandins, collagen and collagenase [15,16]. This initiates a multifaceted, overlapping damage-control process. Mast cells release histamine within the connective tissue and an increase in capillary permeability occurs. Dilated blood vessels carry white blood cells to the damaged areas. The release of interleukins and Transforming Growth Factor Beta (TGFβ), a hormonally active polypeptide, stimulate Connective Tissue Growth Factor (CTGF) and other polypeptide growth factors, which promote cell growth, adhesion, migration and angiogenesis [17,18]. CTGF upregulates the release of MMPs and their inhibitors [19]. MMPs occur naturally within tissues and exert both pro- and antiangiogenic functions. Inflammation accumulates to prevent further damage or destruction of tissue. Finally, through a complex process of interactions, connective tissues utilize nutrients to repair damage as MMP inhibitors help dissipate inflammation. In wound healing, fibrinogen converts to fibrin, thread-like proteins, and forms a mesh-like structure to rebuild tissue. A disproportionate amount (too little or excessive) of inflammation will inhibit repair and remodeling and delay healing. The exact process of remodeling and repair remains unclear and is undoubtedly more complex than described here. As new research is performed, the exact mechanisms mediating these responses may be discovered.

What is known is that the fibroblasts are central to the connective tissue damage response. Also, proteoglycans support repair as they supply the necessary glycosaminoglycans necessary to rejuvenate and create new collagen fibers. Going further, repair also involves the water transport systems as water homeostasis between the ECM, cells and connective tissue must be achieved for proper tissue regeneration.

Collagen fibers

Collagen is the most abundant protein in the human body, and is the dominant protein in the ECM and connective tissue. Collagen, together with elastin, form fibrils of incredible strength: for example, type I collagen is, gram for gram, stronger than steel [20]. Derived from the Greek word for Kolla, meaning "glue", and gen, meaning "producing", its purpose in the body is expansive, from connecting muscles to bones and contributing to tissue and organ stability, to helping tissues withstand stretching and movement without being broken.

Continued research and discoveries in molecular biology and gene cloning have revealed that there are 28 types of collagen in the human body, with the most common being types I, II or III. Both the fibroblasts and epithelial cells make collagen [21]. Together with GAGs and hyaluronic acid, the dermal matrix houses the collagen and elastin needed for a resilient epidermis. Collagen and elastin consist of amino acids, which serve to protect connective tissues (blood vessels, nerves, tendons and ligaments, and dermis) [22]. Also protective, estrogen has been shown to prevent a decrease in skin collagen in postmenopausal women, thus helping to maintain skin thickness. In addition, estrogen increases acid mucopolysaccharides and hyaluronic acid in the skin, which suggests that it could play a role in

maintaining stratum corneum barrier function and connective tissue resilience. It has been postulated that estrogen increases cutaneous wound healing because of its cytokine-regulating role [23]. In fact, topical estrogen has been found to accelerate and improve wound healing in elderly men. Also of note, essential fatty acids and antioxidants act synergistically to moderate the induction of inflammatory mediators, decrease free radical tissue damage, and inhibit collagen and elastin breakdown from MMPs.

Fibroblasts

Fibroblasts are a diverse group of cells that secret collagen. They are part of the family of connective tissue cells that are jointly responsible for maintaining the ECM. Known for their plasticity, fibroblasts play an essential role in the structural framework of the body as well as the stages of wound healing: inflammation initiated by injury, cell proliferation and remodeling [24]. Because fibroblasts are the main cell type found in all kinds of connective tissue and are involved in the regulation of ECM protein production, in aged, diseased or damaged connective tissue, fibroblast activity may be reduced and unresponsive to epidermal growth factor, and this may cause poor wound repair [25]. Studies have shown that oxidative DNA damage contributes to replicative cessation in human diploid fibroblast cells, but this process can be slowed with the use of antioxidants and spin-trapping agents such as alpha-Phenyl-t-Butyl Nitrone (PBN), which can act like an antioxidant [26].

UV radiation has been shown to induce matrix metalloproteinases that can cause ECM degradation, altering the structure of proteins like collagen and elastin and inciting connective tissue disease as well as photoaging and solar elastosis, amongst many other conditions. Several studies have been performed to investigate the role of diet and supplementation to support connective tissue and via free radical defense. Supplementation of the carotenoid beta-carotene has been shown to have protective properties against UVA radiation, which can help reduce the rate of mutation in human fibroblasts after exposure [27]. Astaxanthin, a carotenoid found in microalgae, yeast, krill, and shrimp (to name a few), also demonstrated great photoprotective potential against UVA-induced alterations [27].

Conversely, studies have also shown that fibroblasts use free radicals to stimulate proliferation [28], but this is a complex process involving a balance of precise mechanisms-a process just short of damage. Fibroblasts are active players in adaptive immunity and can transition acute inflammation to acquired immunity through the cells' ability to produce chemokines and the ECM. In response to any damage or injury that results in inflammation, the fibroblasts-which are versatile connective tissue cells and can differentiate into an array of other types of connective tissue cells including cartilage, adipose tissue, bone and even circulate precursors within blood-initiate an adaptive immunity response to commence tissue repair [29].

Proteoglycans

Proteoglycans are a critical, main component of the ECM's ground substance and are important in the regeneration and proliferation of collagen and, thus, connective tissue. Proteoglycans are heavily glycosylated glycoproteins or mucopolysaccharides and are also referred to as Glycosaminoglycans (GAGs). GAGs are predominantly made of hyaluronate and sulfurs, and the ECM contains the largest class of proteoglycans to help hydrate tissue to withstand compressional forces [30]. In skin, proteoglycans support ECM hydration that supports proper fibrous alignment, encourages normal cell turnover and repair, and skin resilience and elasticity [31].

The building block for hyaluronic acid is glucosamine. Studies have shown that the use of glucosamine sulfate long-term can help repair tissue and reduce symptoms in osteoarthritis [32]. Literature also indicates that glucosamine sulfate inhibits ICAM-1 production in conjunctival epithelial cells *in vitro*. It is therefore plausible that future clinical study may show that glucosamine sulfate functions well to abate systemic inflammatory conditions caused by pro-inflammatory cytokines [33]. Sulfur is found in every living cell in the body and it plays a key role in collagen synthesis and immunity [34]. Early studies have also indicated that sulfur-containing foods like garlic, onions, meat, and cruciferous vegetables can offer anti-inflammatory and detoxifying benefits. The sulfur content in GAG molecules allows them to possess a high negative charge density, so they repel each other and cause a space-filling function, permitting them to store water and provide connective tissue with cushioning compression strength and resiliency [35].

Cellular and connective tissue water

Regardless of the precise mechanism of damage or location of damage (e.g., fibroblasts, ECM, collagen) the common pathway to deterioration in all tissues is water loss. It has been suggested that if general cellular health is addressed, simultaneous improvements in systemic, cutaneous and connective tissue health may be seen. This protocol forms the basis of the cellular water principle theory, [36] and the reasoning behind using a multidisciplinary strategy for connective tissue remodeling, repair and damage prevention. The cellular water principle theory builds on Nagy's membrane hypothesis of aging, which discusses cell damage, intracellular waste accumulation, and cell membrane permeability as the result of ROS induced cross-linking and the residual heat formed during heat discharge of the resting potential [37-39]. The cellular water principle develops Nagy's theory, acknowledges that cell deterioration may be more complex, and goes further to suggest ways to slow or reverse cell and connective tissue damage using a systematic, inclusive health program (external, internal and emotional) replete with therapies tailored to a patient's specific needs and aimed at promoting efficient water regulation across all cells and connective tissue [7]. In this way, connective tissue may be more adequately remodeled and repaired while damage is prevented.

Within an inclusive health program congruent with the cellular water principle, cytoprotective therapies, stress reduction, and the inclusion of nutrients (vitamins, minerals and phytochemicals) in the diet are emphasized [40]. Simply, when oxidative stress is reduced and the body is flushed with nutrients topically and systemically, its nutrient-deprived cells and connective tissue can seize nourishment for remodeling and repair [7]. This theory postulates that cell and connective tissue fortifying therapies reduce water loss, but makes clear that the prevention of water loss in tissues goes beyond simply drinking water as it is difficult for damaged cell membranes and connective tissue to retain any water until they are remodeled and repaired. This stabilization of water within cells and connective tissue may increase resiliency to damage offering protection from inflammation, oxidation and MMP formation. Literature indicates that when ICW is addressed, cells are healthy and strong and immunity is functioning at

the highest levels, promoting wound healing and tissue regeneration [41-43]. As a result, optimal cellular and connective tissue conditions are encouraged, plausibly un-complicating and improving overall health.

Treatment and Management Strategies

The human body is a complex, overlapping network of systems, organs, cells, connective tissues and fluids. All systems intersect and rely on each other to maintain body homeostasis. Understanding this, the consideration of using combination therapies featuring nutrition, medication and alternative interventions is a natural choice. Such is the case within our office. We have found that improving connective tissue with singular methods or medications may not function long-term and do not accomplish all treatment goals.

Treatment goals

- Increase cellular and connective tissue immunity
- Reduce inflammation and free radical damage
- Normalize and fortify integument system
- Promote collagen formation
- Address hormonal imbalance and other internal diseases
- Encourage sleep
- Improve nutrition
- Offer relaxation and emotional support

These treatment goals can be achieved using the following three-pronged inclusive approach, which combines multidisciplinary interventions including external care, internal care and emotional care. This mode of treatment encourages cytoprotection and connective tissue fortification from every plausible aspect: [7]

External care: To address innate immunity; strengthen cutaneous defenses to external influences or invaders. Beginning with a daily skin care regimen, external care includes patient-specific cleansers, treatments and hydration to repair damage and protect and fortify the skin's barrier function and connective tissue from external factors such as UV rays. External treatments may focus on collagen-deposition and -formation encouraging agents and treatments.

Internal care: To encourage adaptive immunity. Diagnostic tests assist in determining systemic disease such as endocrine system or vascular disorders, so therapeutic, systemic care can be initiated. Therapeutic care may include nutritional guidance, supplements including sleep-encouraging supplements, physical activity and prescription medication.

Emotional care: To support psychological and social balance. Stress reduction "feel-good" services such as those provided within the spa environment may be used, as well as activities like yoga, support group participation and counseling to nurture the psyche.

External care

A tremendous amount of literature is available on enhancing cutaneous barrier function and protection from environmental aging. No doubt, as each year passes new agents and techniques will be introduced as the skin care industry proves to be an ever-changing market. Current methods include a variety of therapies and a wide range of options that may focus on exfoliation, lipid preservation, sun protection and cosmeceutical use. Topical solutions may feature everything from mechanical devices to chemical agents and botanical ingredients. Combination therapies are the norm with topical procedures and are based on the physician's preference and skill. Some therapies may be used concurrently or in succession for a period of time for ultimate results.

Internal care

Within the body, chronic inflammation can set off a litany of biological responses that may result in cell and connective tissue deterioration or disease. Therapeutic methods to stave off and reduce inflammation utilize nutrients that ensure the tissues have adequate amounts of basic building materials to re-strengthen, abate inflammation, and improve cells and connective tissue turnover. As mentioned previously, these methods include diet and supplements, quality sleep, physical activity and prescription medication.

Diet and supplements

One could surmise that we truly are what we eat. If you performed a complete chemical analysis of your body, the report would read like materials similar to those in foods: fat molecules, carbohydrates, protein complexes, and vitamins and minerals that help you metabolize food and generate the energy you need to live. Think of the body as a self-maintaining factory; it is constantly regenerating itself down to every cell. Each month our skin renews, every six weeks we have a new liver, and every three months we have new bones. To renew and rebuild these organs and tissues, we need to supply our bodies with the elements that have been lost as a result of constant use, degeneration, or aging [44]. In fact, research reveals that aging is a risk factor for malnutrition, with poor nutritional status being one of the major factors associated with mortality in elderly subjects [45]. One way to offset the loss of essential elements is to flood the body with nutrient-dense foods that will strengthen the cells and connective tissue to hold more water [44] through all life stages.

Tissue maintenance and growth is promoted with amino acids [22]. Amino acids are essential building blocks for collagen and elastin, which are crucial in defending connective tissues such as the blood vessels, nerves, tendons, and ligaments. It follows then that a diet rich in amino acids is desirable. Amino acids such as cysteine (precursor of glutathione and taurine) and glycine (precursor of glutathione), methionine (precursor for the sulfur content of cysteine and glutathione) and proline (precursor for collagen) act as (1) building blocks for tissue regeneration and (2) precursors for endogenous antioxidants (in particular, glutathione) [46,47]. Glutathione is a nutrient and essential molecule for protecting cells against oxidative damage, and mediating several metabolic and detoxification reactions [47,48]. It, too, declines with age, making nutritional supplementation essential. Research demonstrates that sulfur-rich foods like broccoli, Brussels sprouts, cabbage and spinach are either high in glutathione or contribute to the production of glutathione. GAGs (glucosamine) and lecithin are also important to add to the diet [49]. Lecithin has been well documented to repair cell walls, thus its focal role in repairing tissues. In fact, lecithin, which is mainly comprised of phosphatidylcholine, is a major component of cellular membranes [50].

In order to initiate remodeling and prevent damage, the incorporation of antioxidants, soluble and insoluble, in the diet is central to reducing the effects of oxidative stress and cellular and connective

tissue water loss [51]. In example, vitamin C removes free radicals from the cell structures composed primarily of water and from areas containing body fluids; beta-carotene and vitamin E are active in the lipid or fatty parts of the cell membrane and in fat tissue; coenzyme Q10 protects mitochondria oxidation; vitamin A plays a large role in the repair of body tissues; and alpha lipoic acid boosts cellular energy, enhances immunity and muscle strength and improves brain function [52-57]. Alpha lipoic acid allows other antioxidants like vitamins C and E to work better, helps detoxify, and even prevents inflammation [58]. A diet rich in these antioxidant nutrients may assist in cellular repair, replication, and prevent oxidation and subsequent damage. Along the same lines, we also suggest an increase in B vitamins because of their known abilities to regulate cellular metabolism and for their immune system support. Additionally, the B vitamins may also play a role in regulating hormones and offering support for the nervous system [59].

Similarly, we also recommend the inclusion of healthful EFAs within the diet with the reasoning that EFAs are found in the stratum corneum and cell membranes. EFAs have been shown to enhance the immune system, thus strengthening the skin's barrier function [60]. Low ratios of omega-6 to omega-3 have been shown to reduce the risk of certain cancers, cardiovascular disease, arthritis and even asthma [61].

The following is a short list of essential nutrients from diet and supplements that are rich in antioxidants, anti-inflammatory agents, collagen builders and other essential nutrients. They assist with the cellular renewal process, help the body hold more water, and can be used in conjunction with an inclusive health program [44].

- Blueberries, raspberries and strawberries
- Goji berries
- Pomegranates
- Vitamin A sources like carrots and mangoes
- Vitamin C sources like kiwis, mangoes, papayas and black currants
- β-carotene sources like carrots, pumpkin, kale and sweet potatoes
- Vitamin E sources like almonds, wheat germ, dark leafy vegetables
- Omega-3, -6, and -9 found in flaxseeds, hemp seeds, cold-water fish, raw walnuts and Brazil nuts
- Lecithin from eggs, cauliflower, oranges, peanuts and tomatoes

Sleep

Perhaps as a side-effect of our sleep-deprived culture, more and more attention is being paid to the importance of sleep, as well as the impact of sleep deprivation or sleep loss. Research indicates that sleep deprivation can alter metabolism, hormone, and immune function, and can impact peripheral tissues such as the skin and lungs [62]. Ample literature exists indicating that sleep loss has the potential to promote degenerative health conditions and poor wound healing [63-67]. In contrast, ample sleep can minimize cellular stress [62]. As such, in our office, we encourage the use of sleep-promoting ingredients such as melatonin and GABA to help fortify cellular immunity [7].

Emotional care

Because of its subjective nature, stress may be difficult for patients and physicians to classify. Scientifically, it has been graded as either acute, episodic acute, or chronic [40]. Advances in technology and our "always on" society have created a new type of stress called Cultural Stress, also known as the syndrome Cultural Stress Anxiety Syndrome (CSAS) [7]. Externally, it is known to produce reactions on skin such as increases in acne breakouts, and it also has internal implications with regard to hormonal imbalance [68]. Systemically, it has been suggested that stress creates microinflammatory pathways [69] and has been linked to telomere shortening which, together, demonstrate a causative relationship, producing cellular deterioration [70].

Mind-body connection

To explore the emotional response within systemic tissues, research has been performed to discover a plausible link between tissue health and the central nervous system. It was found that both the epidermis and central nervous system utilize the same communication molecules, which indicates that there is indeed a mind-body connection or Neuro-Immuno-Cutaneous-Endocrine network (NICE). Specifically, emotions can be used to reduce stress and increase skin health, bi-directionally-mind-relaxing therapies improve skin condition and skin conditioning therapies improve mind relaxation [7,71,72]. Because all systems, tissues, and organs are connected, it can be postulated that stress reduction not only improves skin function and health, but also connective tissue health. In example, massage has been shown to increase the rate of healing, decrease depression, reduce stress, lessen pain, and improve sleep in various studies and reviews [73]. Along the same lines, in our office, certain exercises such as yoga are also suggested to help reduce stress.

Inclusive care program

Within our office, patient-specific inclusive care programs are used to achieve cellular and connective tissue water homeostasis. In this way, we believe that cellular rejuvenation is promoted as is connective tissue repair and remodeling. We do this by assisting patients in enhancing their immune systems and increasing systemic health. Nutritional guidance and dietary supplements are only one aspect of the combination therapy used, and every program is individualized for a patient. To customize the therapy, a thorough analysis of the patient's external, internal, and emotional concerns is performed through a consultation, questionnaire, and blood tests. Baseline measurements are taken and include the use of RJL Systems body composition analysis machines and measurements are taken periodically for the duration of treatment, in addition to questionnaires and photography, offering a tangible record of progress for each case. Based on our preliminary evaluation, a treatment roadmap that outlines external, internal and emotional care is devised.

Prescription medication is discussed and if congruent with the goal of creating optimal systemic health, is suggested. This includes prescription drugs needed to address hormonal imbalance, cardiovascular disease, or chronic inflammation. Further evaluation and treatment by specialists is arranged if necessary. Weekly, if not daily prescriptions for cosmeceutical products and treatments are provided in addition to a schedule of in-house facial, body and massage services. We also provide a detailed dietary and nutritional summary that

outlines foods, nutrients and supplements needed for the patient's body needs, concerns and goals. Likewise, a recommendation for physical activity like yoga, tai chi, walking, etc., is offered to help augment internal treatments while reducing stress levels.

Finally, education is offered regarding the patient's specific health condition(s). Literature is made available, as are referrals to psychological counseling if necessary and/or emotional support groups, if appropriate.

Summary

The human body is a vast network of cells and connective tissue. At the root of all disease, water loss, oxidation, and inflammation cause damage and destroy the components that literally hold the body together. Scientific research on connective tissue-rejuvenating therapies is ongoing. We believe that a combination of therapies may improve overall health, offering patients higher resistance to connective tissue damage. Finally, we feel that rather than singular methods, inclusive treatment in accordance with the cellular water principle may encourage cellular and connective tissue health and positive life-altering changes, improving lifespan. Moreover, the cellular water principle also forms the foundation for larger, more long-term studies on inclusive care methodologies and their correlation with clinically measurable health improvements.

Statement of Conflict of Interest

Howard Murad, M.D., has financial interest in vitamin C, glycolic acid and nutraceutical products distributed and marketed to dermatologists, plastic surgeons and the professional beauty industry under the name Murad.

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