Chapter 1

Anti-Aging Medicine As It Relates to Dermatology

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Core Messages

- Anti-aging medicine physicians, scientists, and researchers are dedicated to the belief that the process of physical aging in humans can be slowed, stopped, or even reversed through existing medical and scientific interventions.
- Possible theories of the aging process include the free radical theory of aging, oxidation, cell senescence, and cleavage of telomere during DNA synthesis.
- A good diet slows the aging process and adds healthier years to life.
- A therapeutic guide for vitamin supplements and recommended anti-aging doses is provided.

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> Old age is the most unexpected of all things that happen to man.
> *Leon Trotsky*

1.1 Introduction

Changes in diet and increasing exercise, together with a regimen of antioxidants, nutritional supplements, and growth factors, can alter how the genes express themselves. Both factors can greatly enhance the healing capability of the skin and can improve the results of cosmetic surgeries.

Beyond the obvious advantages of a balanced diet and exercise there are the physiological ones that help people feel more alive with renewed and vital well-being.

1.2 The Clinical Science of Anti-Aging Medicine

Anti-aging medicine is practiced by physicians, scientists, and researchers dedicated to the belief that the process of physical aging in humans can be slowed, stopped, or even reversed through existing medical and scientific interventions. This specialty of medicine is based on the very early detection and prevention of age-related diseases. Physicians practicing anti-aging medicine seek to enhance the quality of life as well as its length, limiting the period of illness and disability toward the end of one's life. Anti-aging medicine encompasses lifestyle changes (diet and exercise); hormone replacement therapies, as needed, determined by a physician through blood testing (DHEA, melatonin, thyroid, human growth hormone, estrogen, testosterone); antioxidants and vitamin supplements; and testing protocols that can measure not only hormone levels and blood chemistry but every metabolic factor right down to the cellular level.

1.3 The Aging Process

Aging can be viewed as the accumulation of changes in cells and tissues resulting from a greater disorderliness of regulatory mechanisms that result in reduced robustness of the organism to encountered stress and disease. The notion of greater disorderliness in aging is illustrated by the erosion of the orderly neuroendocrine feedback regulation of the secretion of luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH) and growth hormone (GH). These changes are manifested as menopause, andropause, adrenopause, and somatopause.

Skin aging is part of the slow decline in appearance and function that appears to be attributed in large part to the drastic decline of hormones in the body after adulthood. At the cellular level, several processes are involved in the physiology of aging and the development of some age-related diseases. The process of apoptosis signifies the process of nontraumatic and noninflammatory cell death [1].

Dysregulation of apoptosis has been implicated in the increased incidence of cutaneous malignancies that are more prevalent in older individuals, such as basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Cell senescence limits cell divisions in normal somatic cells and may play a central role in age-related diseases. Telomeres are thought to play a role in cellular aging and might contribute to the genetic background of human aging and longevity. It has been speculated that the limited proliferation potential of human cells is a result of the telomere shortening that occurs during DNA synthesis at each cell division. Photoaging may accelerate the shortening of telomeres and push cells into senescence sooner. That could be the reason why various growth factors may affect the speed and quality of wound healing [2]. Biochemical insults also arise within aging cells, in part from the action of reactive oxygen species generated and scavenged incompletely throughout the cell cycle. Aging-associated changes also occur between and among cells via alterations in the intercellular matrix, the intercellular exchange of

trophic factors, the release of inflammatory cytokine mediators, and the degree of infiltration by other associated cell types. In addition, the quantity and distribution of various growth factors may affect wound healing [2]. Decline of DNA repair in combination with loss of melanin increases the risk of photocarcinogenesis and can also cause the decline of enzymatically active melanocytes (10–20% each decade) that contributes to increased sensitivity to ultraviolet (UV) radiation.

However, it is not known why free radical damage does not adversely affect all of the body's cells (e.g., gonadal germ cells) [3].

1.4 Free Radical Theory of Aging

Antioxidizing nutrients are believed to play a role in the prevention and treatment of a variety of chronic diseases. The proposed mechanism by which antioxidants protect cells from oxidative stress is by scavenging free radicals and halting lipid peroxidation chain reactions, which can cause DNA damage [4].

1.4.1 Antioxidizing Processes

Two forms of chemical reactions, oxidation and reduction, occur widely in nature. Oxidation is the loss of electrons, and reduction is the gain of electrons. Oxidation and reduction reactions always occur in pairs. Highly reactive molecules can oxidize molecules that were previously stable and may cause them to become unstable species, such as free radicals. A free radical is a chemical with an unpaired electron that can be neutral, positively charged, or negatively charged. Thus, without termination by an agent such as an antioxidant, a single free radical can damage numerous molecules. A certain amount of oxidative function is necessary for proper health. For example, oxidation processes are used by the body's immune systems to kill microorganisms [5].

Cells contain a number of antioxidants that have various roles in protecting against free radical reactions. The major water-soluble antioxidant metabolites are glutathione (GSH) and vitamin C (ascorbic acid), which reside primarily in the cytoplasm and mitochondria. Many water-soluble enzymes also catalyze these reactions. Glutathione peroxidase catalyzes the reaction between GSH and hydrogen peroxide to form water and oxidized GSH, which is stable [6]. Vitamin E and the carotenoids are the principal lipid-soluble antioxidants. Vitamin E is the major lipid-soluble antioxidant in cell membranes that can break the chain of lipid peroxidation. Therefore, theoretically, it is the most important antioxidant in preventing oxidation of these fatty acids. Vitamin E is recycled by a reaction with vitamin C [7].

Despite the actions of antioxidant nutrients, some oxidative damage will occur, and accumulation of this damage throughout life is believed to be a major contributing factor to aging and disease [6].

1.5 Diet and Nutrition

A good diet slows aging and can improve overall success of surgical procedures and wound healing. Among other benefits, a good diet:

- Provides the food, water, and oxygen that cells need to reproduce, transmit information, and repair damage
- Assures the body of a continuous supply of usable energy, which improves emotional stability and energy levels
- Helps eliminate free radical damage, damage that can increase risk of cancer and other degenerative diseases
- Decreases the risk of cancer, arteriosclerosis, hypertension, heart disease, osteoporosis, senility, and depression
- Synchronizes the body, helping people function physically, mentally, and emotionally at peak efficiency
- Adds healthier years to life

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The diet that will most support healthy longevity follows these principles: It's nontoxic. That means it contains a minimum of preservatives, additives, pesticides, antibiotics, food coloring, and chemical flavoring. The diet should contain enough nutrients to satisfy daily needs. Since most fresh fruits and vegetables lose much of their nutritional value within hours after being picked, it is necessary to supplement with vitamins and minerals.

According to the American Journal of Public Health*, studies show that less than one-third of Americans meet the U.S. government's Healthy People 2000 goal of eating five or more servings of fruits and vegetables per day; people eat only 1.2 servings of fruits and 3.1 servings of vegetables daily.*

Another element of the healthy diet beneficial for women should be soy proteins due to the phytoestrogens that regulate endogenous estrogen production, which is helpful in easing hot flashes and hormonal acne associated with menopause. Topical estrogen induces an increase in skin thickness through proliferation, resulting in decreased rhytids. Scientists at the University of Pennsylvania School of Medicine found that soybeans contain a protease inhibitor called the Bowman-Birk inhibitor, which is so versatile against various cancers that it has been dubbed "the universal cancer preventive agent."

Natural fats provide a concentrated form of energy and create the environment in which fat soluble vitamins can be digested; they also provide the essential fatty acids that the body uses to maintain its cellular structure. Examples of fat are "saturated," from dairy, meat, and fish products; "unsaturated," from vegetable and fish oils; "polyunsaturated,", such as sunflower seed oil and sesame seed oil; and "hydrogenated," such as margarine and highly heated or reheated fats.

The American Heart Association and the National Cholesterol Education Project recommend that the "prudent" diet for everyone, regardless of gender, race, or age, should not exceed 300 mg of cholesterol daily and 65 mg total fat for the person who eats an average of 2,000 daily, inclusive of 22 g of saturated fat.

1.6 Hormonal Regulation of Aging

Aging involves a decline of GH, which causes the immune system response to decline and the amount of oxygen and free radicals to increase. The skin suffers from the consequences of the decline in GH, which is reduced nourishment and repair of cells in the different tissues. The overall functions of the skin decrease with aging. The decline is noted in cell replacement, sensory perception, thermal regulation, and chemical clearance. Also, there is a higher threshold for pain, predisposing to skin irritations, ulcerations, and wounds [8].

Additional changes of skin aging include flattening of the dermal–epidermal junction, which decreases the contact surface between the dermis and epidermis. This change may compromise communication and nutrient transfer between skin layers. There is a decrease in epidermal filaggrin, a protein required to bind keratin filaments into macrofibrils, that contributes to skin dryness and flaking. In addition, there is an increased dermal separation that may cause increased blistering or tearing.

The endocrine system regulates body composition, fat deposition, skeletal mass, muscle strength, metabolism, body weight, and physical well-being. Multiple endocrine changes evolve with aging in all species and, not surprisingly, some of the physiologic manifestations of aging are related to the effects of declining hormone levels. The central nervous system (CNS) regulates the pituitary gland, which secretes hormones to target tissues that, in turn, produce substances that feed back on the hypothalamic–pituitary axis. This feedback-control network can be assessed via novel entropy statistics.

In humans, aging is associated with a decrease in the gonadal production of estrogen in females (menopause) and testosterone in males (andropause), the adrenal production of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEA-S) (adrenopause), and a decrease in the activity of the GH/insulin-like growth factor (IGF) axis (somatopause). Replacing hormones that decline with age had been shown to have a

broad anti-aging and anti-disease effect on the skin and in the body. As a result, hormone replacement regimens are being developed as a strategy to delay or prevent some of the consequences of aging.

1.6.1 Adrenopause

The enzymatic machinery of the adrenal zona reticularis fails in aging men and women. However, the ability of the zona fasciculata to produce cortisol is preserved (based on ACTH infusion, insulin tolerance, and metyrapone testing). Mineralocorticoid and glucocorticoid receptors in the hippocampus are variably down regulated in aging humans. Excessive lifelong adrenal cortisol feedback on the brain may exacerbate the aging-associated loss in neuronal synapses and plasticity. Potential implications of aging skin includes a decrease in vascular responsiveness due to involution of the dermal vascular bed, which decreases thermoregulation and contributes to skin pallor; there is a decrease in subcutaneous fat and changes in distribution that may limit conductive heat loss that decreases the protective ability in bony areas such as the ischial tuberosities; and there is a delayed recovery of the stratum corneum's function as a barrier, which may increase the penetration of certain types of topical medications leading to systemic absorption [9].

1.6.2 Menopause

There is still no known biochemical signal that reliably indicates the onset of menopause. However, serum FSH levels tend to rise in regularly menstruating as well as premenopausal women (42–50 years of age). The pulsatility and orderliness of LH release also change before menstrual cyclicity falters [10]. Estrogen secretion in perimenopause is variable and includes intervals of increased production. A greater stimulation by FSH may increase follicular aromatase activity and induce estrogen excess while inhibin concentrations fall perimenopausally and contribute to heightened FSH release.

Physical complaints such as breast tenderness, irregular menstrual bleeding, dyspareunia, and hot flushes may precede the onset of anovulatory cycles in perimenopause in addition to emotional concerns such as disrupted sleep, fatigue, tension, and irritability, which are equally represented among menopausal women in North America [11]. Skin changes that may occur include hyperpigmentation as well as wrinkles, laxity, pallor, and pruritus. These changes are associated with estrogen deprivation, which leads to decreased skin elasticity and blood supply [12]. Histologically, although the stratum corneum is unaltered in thickness, there is apparently a slow replacement of neutral lipids adversely affecting the barrier function [13, 14].

1.6.3 Andropause

In the hypogonadal male, reduced libido is often accompanied by diminished well-being and/or depression that may be relieved by androgen replacement [15]. Cognitive decline, visceral obesity, osteopenia, and relative sarcopenia also accompany androgen deficiency in aging [16]. These conditions respond favorably to androgen supplementation, especially in men with very low testosterone levels [17]. Enhanced physical performance has not been established in this context. Few studies have examined whether testosterone supplementation enhances cognitive function in elderly men [18]. Although it appears that neoplastic transformation of prostate tissue is not elicited by physiologic testosterone repletion, proliferation of existing androgen-responsive carcinomas may be stimulated. Thus, a normal prostate-specific antigen (PSA) and prostatic digital examination should precede any androgen treatment in older individuals.

Skin decreases in elasticity, extensibility, and turgor. Appendages, including hair follicles, apocrine, and eccrine glands, are decreased in number. Pacinian and Meissner's corpuscles, responsible for pressure and light touch sensation, are similarly decreased. The epidermis may exhibit variable thickness, cell size, and shape with occasional nuclear atypia.

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1.6.4 Somatopause

Gender markedly influences GH secretion in young adults. Premenopausal women exhibit a two-fold less rapid decline than men in daily GH production with increasing age. Young women also manifest less vulnerability to the suppressive effects of increased total body fat and reduced physical fitness on GH secretion [19]. An important ongoing clinical issue relates to the uncertain role of sex-hormone deficiency in the aging-related impoverishment of GH and IGF-I production in both women and men [20]. Preliminary data from clinical studies raise the possibility that combined GH and androgen repletion in older men can have an additive effect on increasing muscle mass [19].

Levels of the nutritional signaling peptide leptin, mostly produced in white adipose tissue, conveys signals to the hypothalamus about fat stores and, in response, hypothalamic efferents regulate food intake and energy expenditure. Leptin inhibits the hypothalamic release of the orexigenic (appetite-inducing) peptide neuropeptide Y (NPY) and activates the sympathetic nervous system. The latter stimulates lipolysis in adipose tissue via the beta-3 adrenergic receptor, cAMP accumulation, and increased activity of mitochondrial uncoupling protein (UCP)-3, thus generating heat (which is dissipated) rather than ATP (which is stored). Leptin-receptor signaling may be attenuated in aging [21].

The aging process causes certain areas of the face to undergo fat atrophy while others experience a persistence or hypertrophy of fat. Fat atrophy occurs in the periorbital, forehead, buccal, temporal, and perioral areas. Fat hypertrophy, however, is seen submentally, in the jowl, lateral nasolabial fold, lateral labiomental crease, and lateral malar areas. The suborbital area may display atrophic changes with concavities and evidence of the underlying orbital rim or hypertrophy with infraorbital fat accumulation and festooning [22].

1.7 Growth Hormone in the Aging Process

GH is the most abundant pituitary hormone. Although GH and prolactin are closely related, GH secretion depends upon hypothalamic stimulation, without which GH secretion falls to low levels and somatotrophs atrophy. Growth hormone-releasing hormone (GHRH), in full sequence a 44-amino-acid peptide, is the principal identified hypothalamic stimulator of pituitary GH synthesis and secretion, activating specific GHRH receptors on the surface of pituitary somatotrophs. GHRH and GHRH-related peptides have a very restricted distribution in the CNS but are also synthesized in gut, pancreas, and gonads, where their physiological roles are still uncertain. Somatostatin [somatotropin-release-inhibiting factor, (SRIF)], a group of 14- and 28-amino-acid peptides, is a potent noncompetitive inhibitor of GH secretion. As with LH and other pituitary hormones, the pattern of GH secretion is episodic, with six to eight pulses per day and very low levels between pulses. Some of these pulses are associated with meals, stress, exercise, or slow-wave sleep. The traditional view has been that the pattern of episodic GH secretion arises from the interaction of GHRH and SRIF secretion modulated by peripheral feedback by circulating IGF-I and other factors.

1.8 Consequences of Reduced Growth Hormone Secretion on the Skin

GH declines with age in every animal species that has been tested to date. In humans, the amount of growth hormone after the age of 21 to 31 falls about 14% per decade, so that the total 24-hour growth hormone production rate is reduced by half by the age of 60. In numerical values, humans produce on a daily basis about 500 µg at 20 years of age, 200 µg at 40, and 25 µg at 80 [23]. The skin of adults with growth hormone deficiency (GHD) is thin, dry, and cool, rendering venous access difficult. These changes probably arise because of the loss of a direct anabolic influence of GH on skin cells exacer-

bated by reduced cardiac output. In addition, GH regulates eccrine sweat glands, and sweating is impaired in GHD, very likely contributing to poor exercise capacity.

Many of the undesirable changes that accompany aging mimic those manifest in the GHD syndrome, including central obesity, muscle atrophy, exercise intolerance, decreased metabolic rate, dyslipidemia, cardiovascular deterioration, osteopenia, thinning of skin, mild anemia, loss of vigor, sleep disturbances, and depression. Aging is thus a partial phenocopy of adult GHD. This has prompted speculation that pituitary somatotroph activity may be a pacemaker of aging and has raised the possibility that GH supplementation might retard geriatric deterioration because replacement therapy reverses most features of GHD in young adults.

Most organic adult GHD arises from pituitary lesions. The loss of GH secretion associated with aging alone results from hormonal changes upstream of the pituitary. Pituitary responsiveness to GHRH persists in aging, although the magnitude of GH release may decline somewhat. The practical implication of this difference is that GH secretagogues should be useful for stimulating GH secretion in normal older people whereas they are ineffective in most organic forms of adult GHD. At any age, including advanced ages; individuals with organic GHD have significantly lower measures of basal and stimulated GH secretion than do age-matched normal subjects [24].

A careful study of the aging face reveals it to be more than just surface textural wrinkling or loose skin. Changes in three-dimensional topography are responsible for the distinctive phenotypic presentation of the face throughout life. These geometric alterations are secondary to apportioning in the fat compartments and result in the fat dysmorphism characteristic of senescence. Redistributing this fat can rebalance the facial fat compartments and mimic the facial structure present in youth [22].

There is no single sign or symptom that is pathognomonic of GHD in adulthood or provides any biological end point for diagnosis. A low serum IGF-I in adults suggests GHD, but a normal value does not exclude the disease. The "gold standard" for establishing a biochemical diagnosis is the peak GH response to insulin-induced hypoglycemia in an insulin tolerance test (ITT). Other GH stimuli such as arginine, glucagon, L-dopa, and clonidine are used in provocative tests, but none is as powerful as the ITT [25]. Despite vast clinical experience with the ITT, controversy remains over what peak GH value constitutes a diagnostic cutoff. Most patients respond to insulin-induced hypoglycemia with a peak GH greater than 5 ng/ml. "Severe GHD" is currently defined by a peak GH less than 3 ng/ml [26]. Because of the lack of standardization of GH assays, each laboratory should ideally establish its own diagnostic threshold values rather than blindly accepting these recommended cutoffs. The diagnosis of GHD is increasingly likely when additional anterior pituitary hormones are found to be deficient, as GH is one of the first of such hormones to be lost in adult hypopituitarism of most causes. Hence, isolated adult GHD should be confirmed with two biochemical tests. Although an ITT is safe when carefully administered, it is contraindicated in the setting of documented ischemic heart disease and seizure disorders [26]. Some investigators do not perform the ITT in anyone over 65 years of age because of potential occult cardiovascular disease (CVD) [25]. In such cases, arginine (or arginine plus GHRH) is probably the best alternative.

Unfortunately, distinguishing organic GHD from the hyposomatomedinemia of aging is a challenge. Although GH secretion is lower at any age in patients with organic GHD than in age-matched normal subjects, the spread between these groups diminishes with advancing age such that GH levels differ by only 13% between elderly adults with GHD and their normal peers [27]. Thus, confirming GHD in an older person may not be possible, especially if only one or no additional pituitary hormones are deficient [25]. The situation is similar for morbidly obese patients in whom GH secretion may be suppressed to a similar degree as in organic GHD. Even among people in whom the diagnosis of normal, age-related, hyposomatomedinemia is clear, the question remains whether such individuals might benefit from restoration of GH to youthful levels.

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1.9 Can Human Growth Hormone Reverse the Effects of Aging?

GH had proven tissue healing effects, and cells regenerate and repair faster, accelerating the process of wound healing in patients injured, severely burned, recovering from surgery, or severely malnourished. All these effects take place through new formation of collagen. The impact of GH treatment on body composition in adult GHD is unequivocal: fat mass and volume are decreased (by 7–15%), with the greatest reductions seen in abdominal visceral depots; lean body mass and skeletal muscle volume are increased (by 5–10%). Most studies showed [28, 29] little change in overall body weight but rather a shift from fat to lean mass [30, 31]. Although the increase in lean body mass can be partially accounted for by GH-induced water retention, observed elevations in total-body K^+ demonstrate that GH also promotes genuine muscle growth. These favorable body composition changes are more pronounced in men than women and more so in young patients with low GH binding protein levels.

Studies of the effect of GH replacement on psychological and social end points in adults with GHD have universally reported a therapeutic benefit [32]. Improvements were found in subjective well-being, mood, energy, sleep, emotional reaction, behavior, pain perception, and overall quality of life [33].

Although adult growth hormone replace therapy is controversial, the initial dose usually recommended is 150–300 ng SQ qhs (approximately 2–4 mg/kg per day). Older patients are started at the lower level of 150 ng, and dose titration should be done monthly or at longer intervals controlling IGF-1 level clinical response, side effects, and individual assessment. The goal dose is based on finding levels of IGF-1 at or slightly below the 50th percentile for age and gender unless side effects are significant. Cancer screening should be done periodically and routinely [34, 35].

At this time, the best therapy against aging is to limit the damage to the DNA with antioxidants, vitamins, and minerals, and try to increase the levels of GH naturally with diet, exercise, and growth hormone releasers.

1.9.1 Growth Hormone Secretagogues

Because the aging-related decline in GH secretion results from changes upstream of the pituitary, hormonal replacement can theoretically be achieved with GHRH or growth-hormone-releasing peptides (GHRPs). There are several conceptual advantages of these therapies over exogenous GH itself [32]. First, even when administered continuously, they preserve the physiological pulsatility of GH release, presumably mediated via intermittent endogenous somatostatin secretion. In addition, the normal negative feedback regulation by IGF-I upon GH release confers relative protection against overtreatment with these agents.

The only GH secretagogue presently approved for use as replacement therapy is GHRH (1–29) NH_2 (Geref, Serono), which has been licensed to treat childhood GHD but is being tested in adults as well. Various GHRPs and nonpeptide GHRP mimetics are also under investigation in elderly subjects [32]. Only short-term trials have been published to date, sufficient to assess only hormonal effects. IGF-I has been raised to youthful levels in older individuals with once- or twice-daily subcutaneous injections of GHRH as well as with infusions or daily oral preparations of GHRPs. Data on body composition and functional end points are being compiled. Side effects resulting from inadvertent overtreatment with secretagogues should be less common than with exogenous GH because of the moderating effects of feedback regulation; studies to date have generally found this to be true. However, some patients do report typical GH-related symptoms of fluid retention as well as allergic reactions at injection sites. Current GH secretagogue formulations delivered transnasally and orally are limited and quite short-acting and therefore are unpredictable. For these compounds to become clinically useful, development of more potent preparations, adjuvants to enhance potency, or synergistic GHRH-GHRP combinations is necessary.

1.10 Side Effects of Growth Hormone Therapy

The side effects of GH therapy arise from the hormonal impact of overreplacement because rhGH is identical to the endogenous hormone and thus should not elicit hypersensitivity reactions, except in the very rare patients with congenital GH gene deletions. Fluid retention due to the antinatriuretic actions of GH is by far the most common untoward effect among adults with GHD receiving replacement therapy. In experimental trials, ~40% of subjects reported clinically apparent edema, ~20% developed joint swelling (especially in the hands) and/or noninflammatory arthralgias, and ~15% suffered from myalgias [36]. Arthralgias probably result from fluid accumulation in joint spaces as inflammatory changes and radiographic anomalies are not found. These side effects are generally mild and resolve within a few weeks of therapy. However, ~10% of subjects develop carpal tunnel syndrome. Increased hypertension is typically not reported even after up to 3 years of treatment. Gynecomastia and atrial fibrillation have occasionally been attributed to GH administration in elderly patients. All GH-related side effects are dose related, and older people are particularly susceptible to them.

As GH directly antagonizes insulin action, a theoretical risk of its use is hyperglycemia. This is a particularly important concern for the elderly as ~40% of people 65–74 years old and ~50% of those older than 80 years have impaired glucose tolerance or diabetes mellitus [36]. Careful studies specifically examining this risk in GHD adults have shown that GH replacement does, indeed, initially decrease insulin sensitivity. However, the effect is reversed within 3–6 months of therapy, and carbohydrate metabolism returns to baseline. This is presumably due to the counteracting effect of losing central body fat and thus increasing insulin sensitivity. Although GH-induced increases in basal insulin or glucose have been seen in some studies, these values generally remained within normal ranges and have never been associated with significant increases in hemoglobin A_{1c}.

Warnings have been voiced that GH could have mitogenic properties. These theoretical concerns derive from highly controversial in vitro data obtained with a variety of cell lineages from the observation that most human solid tumors express IGF-I receptors [37] and from epidemiological evidence that patients with acromegaly have increased incidences of colon and breast cancer [38, 39]. At present, the prudent course of action for patients receiving GH would be to adhere strictly to guidelines regarding prostate examinations and PSA levels in men and breast examinations and mammograms in women. Doctors should also inform high-risk patients of these reports. However, it is inappropriate to extrapolate conclusions drawn from patients with acromegaly who have grossly elevated GH levels to adults with GHD receiving only physiological restitution.

Reports of associations between circulating IGF-I concentrations and the development of prostate and breast cancer have further raised concerns about the long-term risks of GH therapy [40]. However, IGF-I levels in the groups with increased cancer incidences were higher than those that would be sought in carefully titrated physiological replacement therapy. Thus, the applicability of these observations to the latter situation is questionable. Furthermore, there is no strong evidence for increased incidences of prostate or breast cancer in patients with acromegaly, which argues against a causal relationship between IGF-I and these malignancies.

GH administration is currently contraindicated for patients with active malignancy, benign intracranial hypertension, and proliferative or preproliferative diabetic retinopathy [34]. Early pregnancy is not a contraindication, but GH therapy may be discontinued in the second trimester as a GH variant is secreted by the placenta.

One setting in which GH therapy has proved detrimental is in the critically ill. These individuals have impairments of both GH secretion and action. Hence, two randomized, multicenter trials were undertaken to determine whether GH treatment in several hundred intensive care unit patients might speed recovery [41].

Unexpectedly, there was a near doubling of mortality, from 20 to 38%, in both studies.

1.11 A Brief Guide to Anti-Aging Supplements and Growth-Hormone-Releasing Nutrients for the Skin

Updated recommendations, developed in a collaboration between the United States and Canada, incorporate three types of values: the estimated average requirement (EAR), the recommended dietary allowance (RDA), and the tolerable upper intake level (UL). Collectively, these values are referred to as dietary reference intakes (DRIs). EAR is the intake value that is estimated to meet the requirements of a defined indicator of adequacy in 50% of the population (note that this means that the needs of 50% of the population are not being met). RDA is the dietary intake level that is sufficient to meet the nutrient requirements of nearly all individuals in the group. UL is not intended to be a recommended level of intake but represents the highest level of intake that is unlikely to have any adverse health effects in most individuals. It is important to note that the UL is not meant to apply to individuals receiving supplements under medical supervision and should not be used to limit doses investigated in clinical trials [42]. DRIs for antioxidant nutrients were developed by considering the roles of antioxidant nutrients in decreasing the risk of diseases, including chronic diseases and other conditions, and by interpreting the current data on intakes in the United States and Canada.

1.12 Oral Antioxidant Nutrients

In light of new research on the importance of these vitamins to overall health, the Institute of Medicine (IOM) in Washington, D.C., recently released new dietary guidelines for intake of the antioxidant nutrients vitamin C, vitamin E, carotenoids, and selenium. In addition, a variety of other nutrients are believed to be involved in antioxidant processes. According to the IOM, a dietary antioxidant is defined as "a substance in foods that significantly decreases the adverse effects of reactive species, such as reactive oxygen and nitrogen species, on the normal physiological function in humans" [43].

1.12.1 Vitamin C

Vitamin C is the predominant plasma antioxidant. This water-soluble vitamin scavenges plasma free radicals and prevents their entry into low-density lipoprotein (LDL) particles [44]. Vitamin C regenerates active vitamin E and increases cholesterol excretion and improves endothelium-dependent vasodilation and reduces monocyte adhesion. Supplementation with vitamin C (1,000 mg) and vitamin E (800 IU) before the ingestion of a high-fat meal has been found to reverse endothelial dysfunction and vasoconstriction following the meal.

On the skin, the function of vitamin C is the production of collagen, which forms the basis for connective tissue in bones, teeth, and cartilage. It also plays an important role in wound healing, immunity, and the nervous system, and acts as a water-soluble antioxidant. Because vitamin C is water soluble, its antioxidant functions take place in aqueous body compartments. It also helps protect low-density lipoprotein cholesterol (LDL-C) against free radical damage. As an antioxidant, it helps protect against cancer [43], CVD [45, 46], and certain effects of aging [47].

Severe deficiency of vitamin C leads to scurvy, which includes symptoms of bleeding gums, joint pain, easy bruising, dry skin, fluid retention, and depression. Marginal deficiencies may play a role in the development of cancer [48, 49], CVD [50], hypertension [51], decreased immunity, diabetes [52], and cataracts [53]. The RDA for vitamin C is 75 mg/day for women and 90 mg/day for men. Smokers require an additional 35 mg/day due to increased oxidative stress and other metabolic differences. The UL for vitamin C is 2,000 mg/day [43]. It remains possible that higher vitamin C intake may be beneficial in the treatment or prevention of certain diseases, particularly cancer and respiratory disorders.

1.12.1.1 Food Sources

Important sources of vitamin C include citrus fruits, strawberries, kiwifruit, papaya, and vegetables such as red peppers, broccoli, and brussels sprouts. Vitamin C can easily be destroyed during cooking and storage; therefore, food handling and preparation can have a significant effect on vitamin C content.

1.12.1.2 Risks with High Doses

Vitamin C is relatively safe at high doses, but intake of doses higher than 2 g/day may result in diarrhea, nausea, stomach cramping, excess urination, and skin rashes [54]. More recently, 4 g/day has been said to be well-tolerated and safe, except in some patients with renal dysfunction [55]. In rare cases, daily 2-g doses have been associated with kidney stones [56]. Intake of greater than 1 g/day increases oxalate excretion without clinical consequence in normal healthy individuals but could lead to adverse consequences in those with underlying renal disease. Dietary needs of vitamin C are increased by smoking, pollutants, aspirin, alcohol, estrogen, antibiotics, and corticosteroids. It may also interact with various laboratory tests, causing false readings [7].

1.12.2 Vitamin E

Vitamin E is the name given to a group of eight fat-soluble compounds. The most abundant form of vitamin E is α-tocopherol, and this is the only form that is active in humans [43]. However, research suggests that the mixed forms found in food may be more beneficial than the isolated α-tocopherol form that is used in some supplements [7].

Vitamin E supplements are available in natural forms from soybean or wheat germ oil, indicated by a "d" prefix (also referred to as the stereoisomer RRR-a tocopherol), and synthetic forms manufactured from purified petroleum oil, indicated by a "dl" prefix (which includes eight stereoisomers of α-tocopherol, four 2R-stereoisomers, and four 2S-stereoisomers). The most active and available form of vitamin E is α-tocopherol. Vitamin E is the predominant antioxidant in LDL. This vitamin also inhibits platelet activation and monocyte adhesion.

1.12.2.1 Role in the Body and Consequences of Deficiency

The primary role of vitamin E is to act as an antioxidant. Vitamin E is incorporated into the lipid portion of cell membranes and other molecules, protecting these structures from oxidative damage and preventing the propagation of lipid peroxidation [11]. Vitamin E appears to have protective effects against cancer [35], heart disease [4], and complications of diabetes [4]. It is necessary for maintaining a healthy immune system [57], and it protects the thymus and circulating white blood cells from oxidative damage. Also, it may work synergistically with vitamin C in enhancing immune function [5]. In the eyes, vitamin E is needed for the development of the retina and protects against cataracts and macular degeneration [58].

Vitamin E deficiency is rare and occurs mostly in people with chronic liver disease and fat malabsorption syndromes such as celiac disease and cystic fibrosis. It can lead to nerve damage, lethargy, apathy, inability to concentrate, staggering gait, low thyroid hormone levels, decreased immune response, and anemia. Marginal vitamin E deficiency may be much more common and has been linked to an increased risk of CVD and cancer [42].

1.12.2.2 Recommended Daily Allowance

Of the fatty acids, polyunsaturated fatty acids are most likely to undergo oxidation in the presence of oxygen or oxygen-derived radicals. The necessary amount of vitamin E depends on the amount of polyunsaturated fatty acids in the diet. The greater the amount of these fats in

the diet, the greater the risk they will be damaged by free radicals and exert harmful effects. Because it is impossible to obtain a high intake of vitamin E without consuming a high-fat diet, use of vitamin E supplements is often recommended [4].

1.12.2.3 Food Sources

The best sources of vitamin E are certain vegetable oils (including wheat germ oil, hazelnut oil, sunflower oil, and almond oil), wheat germ, whole grain cereals, and eggs.

1.12.2.4 Risks with High Doses

According to the IOM, vitamin E is relatively safe at doses as high as 1,000 mg/day [11], Short-term administration of doses as high as 3,200 mg/day has not been found to be toxic, but adverse effects have been reported with extended intake of 1,100–2,100 mg/day of α-tocopherol [11, 43]. Reported adverse effects include increased risk of bleeding, diarrhea, abdominal pain, fatigue, reduced immunity, and transiently raised blood pressure. Some research suggests that very high doses may be pro-oxidant (i.e., acting as free radicals), especially in smokers [45, 46].

1.12.2.5 Interactions with Other Nutrients and Drugs

Vitamin E exerts antioxidant effects in combination with other antioxidants, including β-carotene, vitamin C, and selenium. Vitamin C can restore vitamin E to its natural reduced form. Vitamin E is necessary for the action of vitamin A and may protect against some of the adverse effects of excessive vitamin A. Because inorganic iron destroys vitamin E, the two should not be taken simultaneously. Cholestyramine, mineral oil, and alcohol may reduce the absorption of vitamin E [44].

Based on the results of a single case report, there has been concern that coadministration of vitamin E with anticoagulants (e.g., warfarin) may enhance their effects [44, 47]. However, a randomized clinical trial that investigated the effects of vitamin E administration in patients on long-term warfarin therapy found no significant change, and the researchers concluded that vitamin E may safely be given to patients receiving warfarin [48, 49].

1.12.3 Carotenoids

Carotenoids (also referred to as carotenes) are a group of more than 600 highly colored plant compounds; however, only 14 have been identified in human blood and tissue [50]. The most prevalent carotenoids in North American diets include α-carotene, β-carotene, lycopene, lutein, zeaxanthin, and β-cryptoxanthin. Only three (α-carotene, β-carotene, and β-cryptoxanthin) are converted to vitamin A and are considered pro-vitamin A carotenoids [11].

1.12.3.1 Role in the Body and Consequences of Deficiency

The only specific effect of carotenoids in humans is to act as a source of vitamin A in the diet, but they also have important antioxidant actions. The latter are based on the carotenoids' ability to quench singlet oxygen and trap peroxyl radicals, thereby preventing lipid peroxidation [50]. As a result, carotenoids protect against the development of cancer, CVD, and ocular disorders. Carotenoids also affect cell growth regulation and gene expression. Diets low in carotenoids may lead to increased risk of cancer and heart disease. Lycopene is the most potent antioxidant for quenching single oxygen and scavenging free radicals [51].

Isotretinoin currently is approved for the treatment of nodulocystic acne, and there have been reported benefits in using 10–20 mg three times a week for 2 months for the treatment of cutaneous aging [59].

1.12.3.2 Recommended Daily Allowance

Currently, there are no DRIs for carotene intake, as it is believed that the current state of research on these nutrients is not strong and consistent enough to support any recommendations. An intake of -carotene 6 mg is needed to meet the vitamin A RDA of 1,000 mcg retinol equivalents (RE) [44]; RE is a measurement of vitamin A intake that allows for comparison of different forms of the vitamin. One IU of vitamin A is equivalent to -carotene 0.6 mcg [60]. Due to insufficient data demonstrating a threshold above which adverse events will occur, no UL has been set for any carotenoid [6].

1.12.3.3 Food Sources

Primary sources of -carotene include carrots, sweet potatoes, pumpkin, cantaloupe, pink grapefruit, spinach, apricots, broccoli, and most dark green leafy vegetables; -carotene is not destroyed by cooking. Lycopene is abundant in tomatoes, carrots, green peppers, and apricots. Lycopene is concentrated by food processing and therefore may be found in high concentrations in foods such as processed tomato products (e.g., spaghetti sauce and tomato paste). Lutein is found in green plants, corn, potatoes, spinach, carrots, and tomatoes, and zeaxanthin is found in spinach, paprika, corn, and fruits.

1.12.3.4 Risks with High Doses

Carotenoids are believed to be safe at fairly high doses. Some areas of skin may become orange or yellow in color (carotenodermia) if high doses of -carotene (30 mg/day or greater) are taken for long periods but will return to normal when intake is reduced [6]. This effect can be used therapeutically in clinical practice to treat patients with erythropoietic photoporphyria (a photosensitivity disorder). Such patients have been treated with doses of approximately 180 mg/day without reports of toxic effects [6]. Carotenes have enhanced bioavailability and have been associated with an increased risk of lung cancer in smokers.

Interactions with other nutrients: Carotenoids require bile acids in order to be absorbed. Conversion of carotenoids to vitamin A requires protein, thyroid hormone, zinc, and vitamin C.

1.12.4 Selenium

1.12.4.1 Role in the Body and Consequences of Deficiency

The most important antioxidant mineral is selenium. Selenium is essential for the function of the antioxidant enzyme glutathione peroxidase, and it is also important for healthy immune and cardiovascular systems. Selenium's anti-inflammatory properties have been demonstrated by its ability to inhibit skin-damaging, UV-induced inflammatory cytokines [61]. Results from a Nutritional Prevention of Cancer trial conducted among individuals at high risk of nonmelanoma skin cancer demonstrated that selenium supplementation is ineffective at preventing skin cancer and basal cell carcinoma and that it probably increases the risk of squamous cell carcinoma and total nonmelanoma skin cancer.

1.12.4.2 Recommended Daily Allowance

The RDA of selenium for men and women is 55 mcg/day, and the UL is 400 mcg/day.

1.12.4.3 Food Sources

Dietary intakes depend on the content of the soil where plants are grown or where animals are raised. Good sources of selenium include organ meats and seafood. Because plants do not require selenium, concentrations of this antioxidant in plants vary greatly, and food tables that list average selenium content are unreliable for

plant foods. In the United States and Canada, the food distribution system ensures that regions with low selenium concentrations in the soil do not have low selenium dietary intakes [6].

1.12.4.4 Risks with High Doses

The UL for selenium is 400 mcg/day; toxicity is noted at mean doses greater than 800 mcg/day, with a 95% confidence limit of 600 mcg/day [62]. Doses above this range result in early symptoms of selenosis, including fatigue, irritability, and dry hair [6, 63, 64]. More advanced symptoms include dental caries, hair loss, loss of skin pigmentation, abnormal nails, vomiting, nervous system problems, and bad breath [63].

1.12.4.5 Interactions with Other Nutrients

The combination of selenium and vitamin E seems to have synergistic effects for the treatment of heart disease, ischemia, and cancer. Vitamin C may also produce synergistic effects, but large doses of vitamin C may result in decreased absorption [65].

1.13 Glycemic Index

Overeating carbohydrate foods can prevent a higher percentage of fats from being used for energy and lead to a decrease in endurance and an increase in fat storage due to insulin. High insulin levels suppress two important hormones: glucagon and GH. The best solution to utilize more fats is to moderate the insulin response by limiting the intake of refined sugar and keeping all other carbohydrate intake to about 40% of the diet. The glycemic index (GI) is a measure of how much insulin increases after eating carbohydrates. High GI foods include sugar and sugar-containing foods, bagels, breads and potatoes, cereals, and other foods containing sugar maltose, as well as oatmeal, bran muffins, pasta, and bananas. Carbohydrates with a lower GI index include pears, natural yogurt, lentils, grapefruit, peanuts, and fructose.

1.14 Final Remarks

When approaching the patient with aging skin, the aim is not to make the skin simply appear smoother or less wrinkled but to make the entire body and mind appear or feel younger.

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