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Review Article

Anti-Aging for Appearance

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Abstract

I suggest that "visual appearance" be included in Anti-Aging Medicine as one of its fields. It is easier to understand "visual appearance" by examining its three components: the physical constitution, appearance, and skin. Morphological changes are the simplest index to assess the level of aging. As we become older: our height decreases; face becomes smaller; and the number of wrinkles increases. Changes in the phenotypic characteristics of humans are presented as aging: from a baby to an elderly person. Changes in the phenotypic characteristics express internal as well as external aging. To examine the mechanisms of aging and Anti-Aging therapies in terms of appearance is to conduct research on the visual aspect of Anti-Aging Medicine and aging itself. As phenotypes, regulated by genes, are also influenced by epigenetic factors, it is very important to focus on the aspect of visual appearance in Anti-Aging research. This review paper discussed aging in terms of visual appearance, including the physical constitution, appearance, and skin based on the relevant literature.

KEY WORDS: Visual appearance, physical constitution, appearance, skin, phenotype

Introduction

Appearance is very important in Anti-Aging Medicine. Appearance is generally considered to be superficial and distinct from the internal state. However, both internal and external aging occur, and there is a close association between them. Therefore, we evaluated appearance according to physique, facial appearance, and skin, which are associated with Anti-Aging Medicine ***(Fig. 1)***.

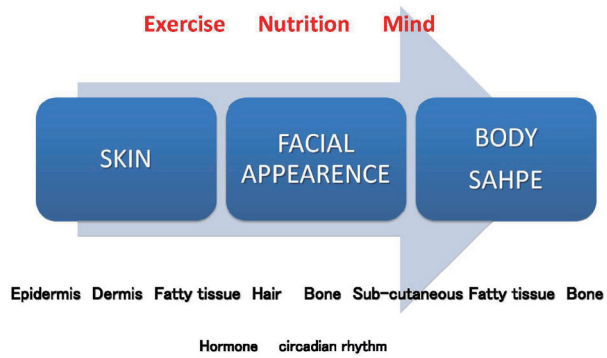

Fig. 1. **Visual appearance**
For Anti-Aging research, Visual appearance include the physical constitution (body shape), facial appearance and skin.

Appearance

The development of cosmetic surgery and cosmetic dermatology has been marked. Sociologically, concerning why people care about appearance, Etcoff [1)] stated that people become unsatisfied with an aged appearance and feel unhappy and develop cognitive dissonance when looking at themselves in a mirror. Stanford [2)] described our times as an era of image. Since visual appearance is important in this era, this field is expected to develop further.

First impressions are deemed lasting, and such impressions are reportedly formed within even a few seconds. What aspects of appearance contribute to a first impression? Basically, appearance includes the items shown in the table. In a broad sense, appearance also includes clothing and accessories, hairstyle, posture, behavior, and voice. It may be difficult to evaluate the whole based on conventional phenotypes such as height, figure, posture, clothing and accessories, facial features, and charm. Unfortunately, many other items require investigation in the future.

Appearance and lifespan

The importance of appearance is well known, albeit tacit knowledge. However, due to its insubstantial nature, appearance has been regarded as relatively insignificant, and beauty has been understood as a superficial, though interesting phenomenon.

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However, extensive studies on appearance and internal aging have been performed since 2009.

Christensen *et al.* [3] reported that perceived age can be a parameter of survival and is associated with telomere length. They performed a follow-up survey in 1,826 twins aged ≥ 70 years and evaluated the association between perceived age and survival, as well as aging phenotypes, and reported that the older-looking twin of a pair frequently died first, and this tendency was more marked in the presence of a greater difference in the perceived age between twins. The results of this study suggest a reflection of biological state in appearance and are encouraging to researchers of appearance.

Colman *et al.* [4] performed an experimental study on long-term maintenance of monkeys with calorie restriction to 70% of normal intake and reported that calorie restriction delayed aging, a finding corroborated by appearance (*e.g.*, personal appearance, physique, and hair) in photos. Restriction of calories to only 70% of normal intake was also associated with low incidences of cancer and cardiovascular disease and high brain function activity. In terms of beauty, as shown in the photos, monkeys on a calorie-restricted diet presented glossy hair and only a few wrinkles (wrinkles around the lower lid, nasolabial folds), only slight sagging, sharp eyes, good skin condition, and a healthy physique with a regular spine, versus those without calorie restriction. In addition, skin aging around the gluteal region was slight. Thus, even the physique, personal appearance, and skin on photos differed clearly.

With studies such as one showing SIR1 gene activation by calorie restriction [5], Anti-Aging Medicine has progressed rapidly. In addition, studies on metabolic syndrome have clarified a signal transmission system from adipocytokine receptors and the existence of an activation system in mitochondria involving the peroxisome proliferator-activated receptor gamma coactivator-1-a (PGC-1) circuit. Mitochondrial activity has a known, important association with longevity genes, while its association with the importance of telomeres for lifespan has been unclear. However, a p53-mediated pathway that connects telomeres and mitochondria has been clarified; telomere shortening inhibits p53 and PGC-1α, β, resulting in a decrease in mitochondria activity [6]. This finding may advance aging research.

Appearance-related research on environmental factors has also been performed. Questionnaire studies of twins have shown that smoking clearly contributes to an aged appearance [7,8], It was also reported that a lower BMI results in a younger appearance until age 40 years, while a higher BMI results in a younger appearance above this age. A longer UV exposure history was reportedly associated with an older appearance, and hormone replacement therapy was reported to result in a younger appearance.

Phenotypes and epigenetics

An important finding in this area is that phenotypes differ when environmental factors including diet differ, even when genetic background is the same. At present, the epigenetic [6] and epigenomic fields are attracting attention. Gene expression is controlled by histone methylation and acetylation and DNA methylation. Gene regulation by microRNA is also being clarified rapidly.

For example, factors inducing methylation include aging and *Helicobacter pylori*. A study on fruit flies also showed that a change in temperature during embryonic development causes a change in eye color to red, and red eyes are inherited even for the subsequent four generations [9]. This finding suggests that acquired characteristics can be inherited, and in this instance, due to environmental factors. A study in rats also showed second-generation inheritance of blood pressure or obesity with metabolic syndrome from males as well as females [10], suggesting that regulation is not simply due to DNA sequence.

In the future, in clinical practice, the landscape of the epigenome will be evaluated using the entire DNA sequence and next-generation sequencers. The landscape will be evaluated before and after not only treatment with a histone deacetylase inhibitor, but also exercise, dietary, and psychological interventions, and methods for maintaining healthy longevity will be performed by gene expression regulation using molecules such as siRNA, depending on the case. Such methods are important for controlling appearance and phenotypes.

Internal and external aging

1. Physique

1.1 Body shape

As shown by the experiment in monkeys, there is a close relationship between aging and physique. In humans too, height decreases with progression of osteoporosis, and an ongoing decrease in muscle strength is observed.

The Japanese lingerie manufacturer Wacoal Corp. performed 3-dimensional measurement of Japanese females over a 45-year period (survey on changes in Japanese women's physique with age) and reported some results on the company home page [11].

The survey was performed during the 45-year period from 1964 to 2009. Of a total of 40,000 adult females who underwent body measurement, subjects included approximately 1,800 women born in the 1950s. A time-series of changes in females born in the 1950s (currently age 50-60 years) showed that the body is slimmest from age 25-30 years, and sizes increase after age 30 years. Changes in the waist and abdomen were the most marked. After age 25 years, waist size increased approximately 10 cm, abdominal circumference approximated bust measurement, and body weight increased by roughly 5 kg. The major changes were as follows: 1) The breasts sagged, 2) the abdomen protruded, 3) the hips sagged, 4) fat accumulated from the waist to the pelvis, and 5) the narrowness of the waist disappeared. Age-related changes in the shape of the breasts and hips occurred, but the order of age-related changes was common, and the age when changes in the breasts and hips started differed among females.

Another age-based study among females, although not a long-term follow-up study like the aforementioned study, showed accumulation of fat in the back, thighs, and gluteal region, a post-menopausal increase in fat in the lumbar region, and accumulation of fat around the abdomen during senescence [12].

It may also be the case that changing societal habits change lifestyle habits, producing changes in physique in a short duration of time. Changes in the physique of Miss Korea winners during a 40-year period were reported, and these changes are of interest with regard to societal changes [13].

The relationship between BMI and physique is also associated with background factors [14] including sex and age. A predisposition to obesity is involved, and there is an inverse correlation between the height and waist in males [15]. Since it is clear that the physique is closely associated with health risks,

future studies will make increasing use of three-dimensional measurement.

1.2 Bone tissue and physique

Bone tissue plays an important role in morphological changes affecting physique and facial appearance. Physique is affected by age-related changes such as curvature of the spine and bone thinning. Facial appearance is also associated with age; specifically, cranial osteoporosis causes sagging of facial features [16,17], and mandibular thinning and decreased dental alveolus cause wrinkles, fine wrinkles, and sagging. We therefore advocate that beauty treatment should first address measures to changes in bone. Bone also plays an important role in glucose and fat metabolism and is therefore involved in the development of diabetes mellitus, metabolic syndrome, and changes in physique. In this context, bone acts as a hormone-producing organ releasing osteocalcin (OC) [18], and estrogen regulates osteoclast formation. Estrogen and Vitamin D also play important particularly important roles after menopause.

1.3 Fat tissue and physique

Bone and fat tissue have each been shown to produce hormones, and physique can be regarded as a phenotype of these functions.

Centenarians show a high adiponectin concentration and high adipocyte sensitivity to insulin. It is possible that the energy metabolism network including fat tissue differs between centenarians and people with metabolic syndrome [19]. Fat tissue function should also be evaluated with regard to subcutaneous versus visceral fat, age, and sex, and further longevity-related studies are necessary.

1.4 Subcutaneous and visceral fat [20]

Body fat distribution is influenced by the balance between active androgen and glucocorticoids in local fat tissue, estrogen, and estrogen receptors α and β [21]. Consequently, post-menopausal females demonstrate accumulation of fat in the back, thighs, gluteal region, and lumbar region, and senescent females demonstrate accumulation of fat around the abdomen [12].

On the other hand, visceral fat is associated with the risks of cardiovascular disease. Type 2 diabetes mellitus is associated with the visceral to abdominal subcutaneous fat ratio [22]. Subcutaneous fat has been reported to decrease disease risks [23], but evaluation including that of the usefulness of ultrasonic or radiofrequency-assisted liposuction and lipodissolve injection is necessary.

1.5 Abdominal and upper body fat

Abdominal fat is considered to increase the risk of metabolic diseases, while fat in the lower half of the body such as the thighs is considered to reduce the risk. The fat accumulation mechanism may differ between the upper and lower halves of the body. The size of each adipocyte increases in abdominal fat, while the number of adipocytes increases in fat in the lower half of the body such as the thighs. This difference may affect physique. It has been speculated that the ability to increase the number of adipocytes in the lower half of the body induces certain defense in the upper half of the body, contributing to the prevention of metabolic diseases such as diabetes mellitus-inducing complications [24].

With age, fat around the thighs also increases. Cellulite [25], an unevenness of skin, is observed in 98% of postmenopausal females in Western countries. Sex hormones are considered to be involved in cellulite formation. Since subcutaneous adipocytes in obesity were suggested to reduce dermal fibroblasts in mice, promoting sagging [26], changes in physique may promote development of cellulite. Most adipocytes were considered to be white adipocytes, but even in adults, brown adipocytes are present around the neck and in the upper half of the body. Since brown adipocytes and myocytes are derived from a common precursor [27], and their energy consumption is marked, there is a possibility that brown myocytes can be used for anti-obesity measures.

Concerning wrinkles associated with major sagging, a gene responsible for wrinkles in Chinese Shar-Pei dogs was clarified [28]. This is a hyaluronic acid-related gene, and its association with periodic fever syndrome has also been suggested. Its association with inflammation [29] is also suspected. In the future, many wrinkles causing an appearance older than chronological age may be explained by not only UV rays, but also inflammation.

2. Facial appearance

Osteoporosis of facial bones is the most important factor in deterioration of facial appearance [16]. Parameters of facial appearance include hair pattern, sagging, and deep, moderate, and fine wrinkles. The cranial bones, particularly facial bones themselves, are wizened by osteoporosis and demonstrate mandibular changes and narrowing. The orbits also enlarge, causing sagging reflected by eye drooping and blepharoptosis. In this sense, after menopause, estrogen replacement should be particularly considered.

For slight sagging, radiofrequency skin tightening was developed in 2002, and stable results were reported in 2007 [30]. Apparatuses in the field in phototherapy including that with infrared rays have been developed rapidly, and more useful apparatuses may be developed in the future. For the treatment of nasolabial folds, muscle relaxation using Botox may also be useful. Its application for depression was also reported. Formation of a smile may be effective for brain activation, controlling the central nervous system [31,32]. In recent years, Botox has been used externally, and progress in this field has also been observed.

Concerning the development of general wrinkles, both UV exposure and aging induce reactive oxygen production, disrupting collagen, while collagen disruption and degeneration result in reinforcement of reactive oxygen species [33].

Cured-type fillers containing hydroxyapatite reproduce tissue resembling bone, and correction of the narrowing of the lower orbit with these fillers is possible in the field of cosmetic dermatology. After filler application, fibers induce collagen production by cells, and, indeed, the duration until the next filler injection due to marked wrinkles is prolonged [34]. A decrease in collagen with age is well known. However, whether this decrease should be evaluated at the physique level or skin level is difficult to determine. Hydroxyproline can be confirmed in the blood after gelatin intake [35]. and collagen is produced after the addition of gelatin to fibroblasts [36]. These findings suggest that collagen peptides will be a promising field.

The nucleoside analogue reverse transcriptase inhibitor (NRTI) used in anti-HIV treatment promotes aging and causes an aged appearance. Concerning its mechanism, it has been clarified that MRIT treatment does not increase the mtDNA mutation rate but markedly amplifies mtDNA, and the resulting clonal expansion of mutations occurring due to general aging in muscle fibers promotes aging [37].

Hair is also an important field. Androgenetic alopecia (AGA) has been studied extensively [38]. Enzyme inhibitors are used for AGA, and certain results have been obtained. Although the mechanism of poliosis has not been clarified, studies on stem

cells have shown the involvement of changes to pigment cells and hair matrix cells from their respective stem cells [39,40].

3. Skin

The development of wrinkles and spots due to UV rays has become well understood, and reactive oxygen generation is associated with spots and wrinkles in the epidermis and dermis [41].

It is appropriate to classify skin aging into a poor texture, fine wrinkles, moderate wrinkles, deep wrinkles, and sagging. Since their causes are considered to differ, coping methods may also differ.

Poor texture and fine wrinkles are associated closely with external factors, particularly UV rays. Not only conventionally confirmed wavelengths but also infrared rays have also been reported to be involved in wrinkle formation. Therefore, visible rays should also be evaluated as the cause of fine wrinkles in the future.

On the other hand, a decrease in dermal collagen is associated with a decrease in TGF-b, the photoaging pathway, and changes in the extracellular matrix associated with saccharification. A decrease in dermal collagen reduces elasticity. For the comprehensive understanding of these, there is a concept called dermatoporosis [42]. Personally, we assume the following slightly broader concept: Aging of all of the epidermis, dermis, and subcutaneous fat induces, for example, senile purpura. Although no abnormalities in coagulation factors are observed, subcutaneous bleeding is noted in the absence of trauma. In such cases, although the disruption of subcutaneous collagen fibers due to UV rays is important, the involvement of the fragility of blood vessels themselves and a decrease in the function of vascular innervation are also involved. Not only epidermal drying but also factors in a broad range such as a decrease in elasticity and vascular and nerve problems are involved.

The association between osteoporosis and aesthetics is important, which may be mediated by vitamin D. In depression, circulatory diseases, and diabetes mellitus, the blood vitamin D concentration decreases particularly at an age over 50 years. From this aspect, UV exposure is necessary for vitamin D activation. However, in the skin, since UV rays cause skin cancer, and both UVA and UVB are involved in the degradation of dermal collagen and elastic fibers, the association with light is an important problem. At present, both UVA and UVB should be avoided, and when 25(OH)D in cannot be acquired through diet, oral vitamin D intake is recommended [43,44]. To improve dermatoporosis, the control of only the epidermis and dermis is inadequate, and consideration should be also given to nerves, blood vessels, and fat in the aged skin. For this, measures for the entire body are necessary.

Conclusions

From the viewpoint of Anti-Aging in terms of appearance, internal aging is connected to external aging, and a healthy state is associated with an aesthetically favorable condition. To pursue beauty is to pursue health, and vice versa.

Conflict of interest statement:

The authors declare no financial or other conflicts of interest in the writing of this paper.

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