REVIEW ARTICLE

Full Scope of Effect of Facial Lipoatrophy: A Framework of Disease Understanding

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BACKGROUND Facial lipoatrophy has been observed to occur in a variety of patient populations, with inherited or acquired disease, or even in aging patients as a natural progression of tissue change over time. There is currently no framework from which physicians of all medical specialties can communally discuss the manifestations, diagnoses, and management of facial lipoatrophy.

OBJECTIVE The aim of this assembly was to derive a definition of facial lipoatrophy capable of being applied to all patient populations and develop an accompanying grading system.

RESULTS The final consensus of the Facial Lipoatrophy Panel encompasses both aging and disease states: ''Loss of facial fat due to aging, trauma or disease, manifested by flattening or indentation of normally convex contours.'' The proposed grading scale includes five gradations (Grades 1–5; 5 being the most severe), and the face is assessed according to three criteria: contour, bony prominence, and visibility of musculature.

CONCLUSION Categorizing the presentation of facial lipoatrophy is subjective and qualitative, and will need to be validated with objective measures. Furthermore, during the assembly, several topics were exposed that warrant further research, including the physiology of volume loss, age and lipoatrophy, and human immunodeficiency virus and lipoatrophy.

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The etiology of facial lipoatrophy has been attributed to specific disease states, both inherited and acquired, the treatment of certain diseases, and as a result of the natural course of aging. The Facial Lipoatrophy Panel was united by the recognition that the community of physicians treating facial lipoatrophy lack a shared vocabulary with which to discuss the full range of presentations, diagnoses, and treatments for the condition. The absence of a common panspecialty language could hinder the exchange of information, ideas, and research from one area of medicine to another. Given the psychosocial impact facial lipoatrophy can have on affected individuals, this interest in sharing

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knowledge and expertise is more than an academic concern.

To represent the full range of knowledge and expertise on lipoatrophy, the Panel comprised an international assembly of physicians from a number of medical specialties, including dermatologists, plastic surgeons, cosmetic surgeons, and endocrinologists. The Panel's collective experience encompasses both the full extent of conditions that may give rise to facial lipoatrophy and the entire spectrum of severity.

The first major aim of the Panel was to derive a definition of facial lipoatrophy that extends beyond the literal meaning of the word to encompass all patient populations. The second aim was to develop a grading system for facial lipoatrophy. An accepted and validated grading system would aid communication between physicians by acting as a convenient form of shorthand. Furthermore, the widespread adoption of a single scale would render results generated by different investigators more readily translatable into the wider context of research. The developed scale was plainly worded intentionally for purposes of inclusiveness: physicians should be able to use the scale when discussing with a patient the extent of intervention required, and patients should feel fully involved in their treatment.

The development of a grading system for facial lipoatrophy is not without precedence; however, existing scales are not universally applicable. For example, a scale has been developed by James and colleagues for human immunodeficiency virus (HIV) specialists to describe the extent of HIV-associated lipodystrophy, of which facial lipoatrophy is only one component.[1,2] The scale developed by James and colleagues[3] was specifically designed to grade facial lipoatrophy, but was developed exclusively for use in populations of HIV-infected individuals and focuses on only one area of the face (the cheeks). Although the buccal areas are most frequently affected by facial lipoatrophy, there is great variability in individual presentation of lipoatrophy: cheeks may not be affected, and other affected facial regions would not register on this scale. In addition to cheek and temple volume losses, there may be accentuated facial folds, protruding facial musculature, prominent veins, and bony landmarks. The integrated facial lipoatrophy grading scale developed by the Panel captures the mildest to the most severe manifestations of the condition and encourages the physician to examine the patient for all signs of lipoatrophy: not only areas of depression but also the appearance of visible facial musculature and bones that would not be prominent otherwise.

Although it is hoped that the subjective facial lipoatrophy grading scale could be used routinely in the clinic, objective means of evaluating dermal and subcutaneous fat thickness are not routinely used in this context. Techniques that do provide direct measures of skin thickness, such as ultrasound, were discussed by the Panel in light of their applicability for use in clinical trials of products designed to correct facial lipoatrophy.

The process of establishing a universal definition and integrated grading scale of facial lipoatrophy generated lively discussion and debate among the Panelists, such that a number of key areas that warrant future research were identified. It is hoped that this publication will not only stimulate wider debate but also greater cooperation between the many specialists involved in this treatment area.

Overview of Lipoatrophy

Facial lipoatrophy is one of the many features of the normal aging process that occurs in healthy adults, which perhaps explains why it is an accepted but seldom discussed phenomenon. Lipoatrophy, however, is also a manifestation of lipodystrophy, whereby metabolic disturbances lead to abnormalities in adipose tissue. Diseases that cause lipodystrophy can be inherited or, more commonly, acquired, and lipodystrophy can either be localized (partial) or involve the entire body (generalized).[4] The challenge faced by the Facial Lipoatrophy Panel was to generate a meaning-

ful defining description of facial lipoatrophy that could be universally applied across all patient populations.

Inherited Lipodystrophy

Most inherited lipodystrophies that have been genetically characterized are autosomal-recessive conditions, as exemplified by the two types of congenital generalized lipodystrophy: Type 1 (involving the *AGPAT2* gene) and Type 2 (involving the *seipin* gene). Both diseases are associated with extreme generalized absence of adipose tissue throughout the body, resulting in a muscular appearance. Similarly, the two types of mandibuloacral dysplasia are autosomal-recessive disorders involving partial lipodystrophy. These partial lipodystrophies are characterized by skeletal anomalies and either loss of fat from the arms, legs, and trunk (Type A) or a more generalized loss of fat (Type B). Conversely, familial partial lipodystrophy is an autosomal-dominant condition that manifests as progressive fat loss and redistribution at puberty; depending on the genes involved, lipoatrophy may or may not involve the face, although fat loss from the arms and legs is always present.[4]

A number of other lipodystrophies have been described, for which the etiology is not yet known, although some level of genetic involvement is thought likely. Progressive facial hemiatrophy, or Parry–Romberg syndrome, is an extremely rare condition characterized by unilateral atrophy of the skin, dermis, fat, and underlying bony structures. This syndrome has many features in common with linear scleroderma "*en coup de sabre*" (LSCS), but is distinguished by more extensive involvement of the lower face with only slight cutaneous sclerosis.[2]

Acquired Lipodystrophy

Acquired lipodystrophy can also be categorized into four subgroups.[4] The first disorder, generalized lipodystrophy, is often associated with immune-mediated diseases, such as juvenile dermatomyositis, and typically presents in childhood or adolescence. Fat loss can occur throughout the body, although the greatest depletion occurs peripherally in the face, arms, and legs. Similar to generalized lipodystrophy, partial lipodystrophy (Barraquer–Simons syndrome) is characterized by autoimmune-mediated adipose loss with fat redistribution and also manifests during childhood and adolescence. The upper body, including the face, upper abdomen, neck, arms, and thorax, present with fat loss, while excess fat is found in the legs and hips. Localized lipodystrophy, the third subgroup of acquired lipodystrophy, is generally characterized by small indentations of fat loss, often related to drug injection via pressure-induced atrophy of adipocytes or local immune-mediated processes. To date, however, the most prevalent acquired lipodystrophy, which can involve severe facial lipoatrophy, is found in patients infected with HIV.

HIV-associated Lipodystrophy

Recently, there has been an increase in the reported incidence of severe facial lipoatrophy in HIV-positive patients, with researchers reporting extreme facial adipose loss where there is no detectable fat layer.[5,6] As a result, patients variably present with sunken cheeks and temples, accentuated facial folds, protruding facial musculature, bony landmarks, and prominent veins on the legs. Facial lipoatrophy in HIV patients is a facet of lipodystrophy, which affects the limbs, the lower abdomen, and the back. The pathogenesis of HIV-associated lipodystrophy, of which facial lipoatrophy is only one feature, is not entirely understood. Research suggests an association with highly active antiretroviral therapy (HAART),[7,8] which was introduced in the mid-1990s for the management of HIV. HAART is a combination treatment regimen usually comprising two classes of antiretroviral, with each class targeting a different phase in the HIV replication cycle. Successful treatment can lead to decreases in plasma HIV viral loads to undetectable levels, increases in CD4 counts, and fewer opportunistic infections. Due to HAART's success in reducing mortality and morbidity rates,[9] it is considered

the mainstay for HIV management. Thus, HIV can now be viewed as a chronic disease, stabilized by long-term HAART.

In patients who are otherwise healthy, the emaciated appearance resulting from lipoatrophy can have a devastating psychosocial impact. Low self-esteem, depression, feelings of loss of control, relationship problems, fear of stigmatization, decreased sexual activity, and social isolation can result from lipoatrophy, to the extent that the patient may become noncompliant with HAART or even discontinue therapy.[10–14] Therefore, treatment of facial lipoatrophy not only represents physical volume correction of the symptoms of the condition, but also a means of improving patient quality of life.

The degree to which HIV-associated facial lipoatrophy can be corrected is dependent on a number of factors. In some patients, neocollagenesis may be minimal, therefore, limiting the correction that can be achieved with those products that illicit a foreign body reaction. Any correction must also be focused on those areas from where volume was first lost. Correction can also be maximized if the patient has thick skin. Correction in those patients with thin skin can be limited. Adequate restoration of volume also depends on where on the face lipoatrophy has occurred; cheeks are more responsive than temples, for example. Temporal factors are also important as correction is achieved after the first treatment, but this initial volume restoration is due to swelling. True correction with some products can take many weeks or months.

Aging Patients

Facial lipoatrophy is also a natural, biologic process that begins at age 20,[15] becoming noticeable from approximately 30 years of age, in the majority of the population. Many other changes also occur in the aging skin: collagen levels decline,[16] as do levels of certain glycosaminoglycans,[17] while it is typical for certain facial areas to gain subcutaneous adipose tissue.[15] Changes also occur in the cranial skeleton as a result of senescence. Although material and structural bone strength are maintained in early adulthood by remodeling, with age, less new bone is formed than resorbed at each site remodeled, resulting in bone loss and structural damage.[16] Consequently, the loss of bone, redistribution of fat, and decreased dermal elasticity and thickness contribute to the sagging of the skin.[18]

As is the case in patients with HIV-associated lipoatrophy, facial lipoatrophy can distress the aging patient, resulting in a reduction of self-esteem and self-image, depression, and social isolation.[19,20] Therefore, patients will often seek corrective procedures to change their physical appearance in order to achieve certain psychosocial goals.[20]

Definition of Facial Lipoatrophy

The meaning of "lipoatrophy" can be derived from the word itself, but this definition does not capture the range of diseases and processes that may give rise to the condition, as described above. The final consensus of the Facial Lipoatrophy Panel was a definition that encompasses both aging and disease states: *Loss of facial fat due to aging, trauma, or disease, manifested by flattening or indentation of normally convex contours.*

Measuring Facial Lipoatrophy

There is currently no consensus as to how facial lipoatrophy should be most usefully measured. The increase in the number of HIV-infected individuals with the distressing stigma of facial lipoatrophy, along with a growing number of products that promise to add volume to recontour the face, has generated interest previously lacking in this area. The lack of universally validated diagnostic criteria, and tools with which to measure the severity of facial lipoatrophy, has created a number of distinct difficulties. First, it is problematic to compare and synthesize data generated by multiple investigators if there is no standard and accepted method with which to measure lipoatrophy. Second, a means of comparing the thickness of facial tissue layers, before and after treatment, is re-

quired to inform patients of relative treatment efficacy. Third, without diagnostic guidelines, judgment as to who should receive treatment for lipoatrophy (and benefit most from it) becomes subjective and thus open to criticism.

The measurement of subcutaneous fat may appear to be the most relevant parameter when evaluating facial lipoatrophy; however, this approach does not consider the mechanisms by which treatments improve the appearance of this condition. Although fat transfer directly replaces lost fat, other techniques create volume within the dermal layers to correct the appearance of lipoatrophy. Therefore, the ideal measurement technique would quantify the depth and volume of the epidermis, dermis, and subcutaneous fat. Further desirable properties include ease of use, affordability, noninvasiveness, and a high level of safety assurance.

A number of techniques have the potential to measure dermal and subcutaneous thickness and provide the most appropriate capabilities for measuring facial lipoatrophy and its treatment progression: X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound. A new technique, computerized topographical mapping, which will be discussed in greater detail under "Future Research," also offers promise in this area.

Measurement Techniques

X–Ray The application of new digital X-ray techniques enables the skin, fat, and muscle of patients to be clearly visualized. Modern equipment creates X-ray films from a standardized distance and transfers the images to composite video for digitization. This technique facilitates the measurement of many craniofacial parameters. Although bone, skin, fat, and muscle are clearly visible, the technique does not directly measure tissue depth. Furthermore, this imaging technique can only be used to study the face in profile and exposes the patient to unnecessary ionizing radiation.

CT CT is another radiographic technique widely applied in many areas of medicine. Multiple X-ray images are assimilated into a two-dimensional cross-sectional image, revealing many soft-tissue structures not shown by conventional radiography. Because subcutaneous adipose tissue is less dense than water, it can be discerned from muscle and dermis,[21] although the technique is not sensitive enough to differentiate the epidermis from the dermis. CT imaging, however, is designed to quantify volume rather than depth.

MRI MRI employs similar computational analytical techniques to CT scanning, but is able to distinguish adipose tissue from other tissues on the basis of differential proton movement, rather than defined X-ray attenuation values.[21] Using the latest techniques of combining high-resolution MRI with improved microimaging methods, the stratum corneum, epidermis, papillary dermis, reticular dermis, and hypodermis can be visualized and quantified.[22] Disadvantages of MRI include lengthy scanning times[22] and the inadvisability of performing the procedure on patients more frequently than every 6 months, which could limit its use in clinical trials.

Ultrasound In contrast to MRI, CT, and X-ray, ultrasound is simple to use, fast, and does not involve patient exposure to electromagnetic radiation. With ultrasound, sound waves penetrate the body, hitting contiguous interfaces of the skin. At each tissue interface, a fraction of the sound energy is reflected back. The reflected component (echo) is received by a transducer and converted into an electric pulse for computational analysis, thus permitting the visualization and quantification of superficial soft tissue. This technique has recently been employed in two trials designed to assess the efficacy of injected poly-L-lactic acid (PLLA) in patients with lipoatrophy (the VEGA Trial and the Chelsea and Westminster trial).[5,23]

The VEGA Trial A total of 50 patients with severe HIV-related facial lipoatrophy were recruited into the VEGA trial. Patients received four sets of PLLA injections, 2 weeks apart, for 6 weeks. Using ultrasound, measurements of total cutaneous thickness

(TCT) were taken before treatment (baseline) and at Weeks 6, 24, 48, 77, and 96.[5] The primary endpoint was defined as the proportion of patients with a significant improvement in baseline TCT ($\geq$10 mm) at the nasolabial fold at Week 24. For each patient, the TCT measurements were summarized by the mean of the minimal and maximal value for each cheek.

Two advanced sonography machines (Logiq 9 and Logiq 7, GE Medical Systems, West Milwaukee, WI) were used in the trial, both of which were operated at transducer frequencies of 7.5 to 13 MHz. Speckle reduction imaging was used to enhance images by improving detail and contrast, and crossbeams enhanced the accuracy of measurements taken. Blood-flow information was also generated using a power echo Doppler. To obtain the most reliable measurements of dermal thickness, generous amounts of gel were used to avoid pressurizing the skin. The same position on either side of the face was analyzed for each patient (corresponding to the nasolabial area below the malar bone and above the masseter muscle), and at each assessment, the mean of three measurements was taken. For consistency, all ultrasound assessments were performed by the same operator.[5]

Before treatment, it was found that the population studied had no subcutaneous fat in the area of the face examined, whereas normal measurements are 1,500 to 4,000 μm for the hypodermis, 1,200 to 1,800 μm for the dermis, and 50 to 100 μm for the epidermis.[24] Although PLLA treatment did not affect fat, facial volume was improved by increasing TCT. At Weeks 6, 24, 48, 77, and 96 of treatment, the proportion of patients with TCT >10 mm increased from baseline by 19, 41, 61, 52, and 43%, respectively ($p<.001$ vs. baseline at all assessments). As would be expected, immediately after injection, PLLA caused a temporary inflammatory response. Interestingly, the rate of inflammation decreased as the study progressed, such that by the end of the study, 1 to 2% of patients experienced postinjection inflammation, both according to the Doppler assessment and patient-reported outcomes.

PLLA increased volume at the interface of the dermis and subcutaneous fat layer, as noted on the ultrasound images by the presence of a distinct layer that resembled neither adipose tissue nor the dermis. Unfortunately, without biopsy, the nature of this area could not be determined.

Modern ultrasound devices and equipment can provide useful measurements of skin thickness. Other methods also have their place: MRI provides excellent images relevant to the dermatologist/surgeon, but is prohibitively expensive and not routinely available; and CT scans and X-rays produce useful volume rendering results, but are less applicable for the measurement of skin depth. Anthropometric approaches, such as calipers, are prone to systemic error and do not provide visual information, but are cheap, safe, and easy to use. Advanced photographic three-dimensional microtopography imaging systems may become a useful addition to the currently available techniques applied to measure lipoatrophy.

Grading Lipoatrophy

Previous grading scales for lipoatrophy have focused on its occurrence as one of many factors (demographic, clinical, metabolic, pharmacologic) of HIV-associated lipodystrophy.[1,2] For example, the scale developed by James and colleagues[3] represents the first effort to specifically categorize facial lipoatrophy as a unique condition. This scale is limited to facial lipoatrophy as a consequence of HAART treatment for HIV[3] patients and focuses on only one area of the face where lipoatrophy might occur (the cheeks).

It was the intention of the Facial Lipoatrophy Panel to develop a grading scale of facial lipoatrophy that could be applied according to the inclusive definition described earlier. As such, the new grading scale would have to embrace the extent and types of lipoatrophy caused by inherited and acquired diseases, as well as the aging population. Therefore, the proposed scale describes patients

ranging from those with mild facial contour flattening due to age-related lipoatrophic volume loss to the most severe pathologic facial lipoatrophy patients, such as HAART-treated HIV patients.

The Facial Lipoatrophy Panel considered the utility of the scale to be of foremost importance, such that every physician, from whatever specialty, should be able to easily diagnose a lipoatrophic patient according to the outlined grades. The assigned facial lipoatrophy grade should then be translatable from one physician to the next, providing a valid and reliable platform for discussion or treatment. Furthermore, grade descriptions should be easily understood, and economically and plainly worded, so patients may understand and actively participate in their assessment and treatment.

The agreed scale includes five gradations (Grades 1–5; 5 being the most severe) with an implied initial gradation of 0 for those patients without facial lipoatrophy. Grades 1, 3, and 5 are specifically described in detail and represent mild, moderate, and severe changes; Grades 2 and 4 represent intermediate degrees of severity to adjacent Grades and have been intentionally left without specific description. This design allows for the expected variability in regional symptom presentation, providing the physician with a flexible scale, applicable to all patients, regardless of lipoatrophy severity.

In the proposed grading scale, the face is assessed according to the following three criteria: contour, bony prominence, and visibility of musculature. The anatomic regions of contour assessment are the cheek (consisting of the entire midface not described by another region), temple, and preauricular, perioral, and periorbital areas. The detection of specific bony prominences is intended to aid in assessing the degree of atrophic change, but is not an absolute criterion for a given grade. Typical bony landmarks include an increasingly apparent zygomatic arch, bony orbits, visible detail of the maxilla and mandible, or any other uncommon bony appearance not usually observed in nonlipoatrophic patients. Similarly, visible musculature is not necessarily required to meet the criteria of a grade, but is a helpful guide to the degree of atrophic change. Visible muscles could include the zygomaticus major, zygomaticus minor, risorus, levator labii superiorus, obicularis oculi, masseter, and temporalis muscles or additional muscles otherwise visibly uncommon in nonlipoatrophic patients.

Figures 1–5 provide a visual guide as to each grade. For each grade, an example of a male and a female, both in profile and straight on, have been given, so all areas of lipoatrophy can be visualized. The use of photographs has been avoided because of the inherent difficulty in obtaining sufficiently standardized photographs. Many members of the Panel felt that the

Figure 1. Grade 1 facial lipoatrophy.

Figure 2. Grade 2 facial lipoatrophy.

ethical issues involved in using actual patient images to exemplify a grade of lipoatrophy could be problematic, particularly because the most severe grades of facial lipoatrophy are typically found in HIV-infected patients.

Grade 1 (Figure 1)

- Mild flattening or shadowing of one or more facial regions (including the cheek, temple, preauricular, periorbital, and periorbital areas).
- No prominent bony landmarks.
- No visibility of underlying musculature.

Grade 2 (Figure 2)

- An intermediate point between Grade 1 and Grade 3.

Grade 3 (Figure 3)

- Moderate concavity of one or more facial regions (including the cheek, temple, preauricular, periorbital, and periorbital areas).
- Prominence of bony landmarks.
- May have visibility of underlying musculature.

Grade 4 (Figure 4)

- An intermediate point between Grade 3 and Grade 5.

Grade 5 (Figure 5)

- Severe indentation of one or more facial regions (including the cheek, temple, preauricular, periorbital, and periorbital areas).
- Severe prominence of bony landmarks.
- Clear visibility of underlying musculature.

Future Research

The discursive process of developing a consensus of the definition and grading of facial lipoatrophy exposed areas in which knowledge is currently

Figure 3. Grade 3 facial lipoatrophy.

Figure 4. Grade 4 facial lipoatrophy.

lacking. Several topics that warrant future research were identified by the Facial Lipoatrophy Panel. Those that directly relate to the definition, grading, and measurement of facial lipoatrophy include validation of the developed grading system, correlation of the grading system with objective measures of facial lipoatrophy, and validation and correlation of objective techniques of measuring facial lipoatrophy. It also became clear that there are some fundamental gaps in existing knowledge concerning the physiology of facial lipoatrophy, both as part of HIV-associated lipodystrophy and in the context of the more general facial volume loss that occurs with age.

Physiology of Volume Loss

Although some useful parallels can be drawn between facial lipoatrophy caused by age and illness, it can be assumed that the physiologic processes that lead to fat loss are analogous rather than homologous, given that individuals with HIV-associated facial lipoatrophy do not present with the same pattern of fat loss as those whose visage has altered with age. For example, although nasolabial folds and buccal fat loss are common features of both conditions, patients with age-associated lipoatrophy frequently present with a flat vermilion border and reduced lip volume, a feature seldom identified for correction by patients with HIV-associated lipoatrophy (unless they are also old). Moreover, aged patients present with a range of other features caused by more general volume loss, in addition to lipoatrophy. Nevertheless, the mechanisms underlying lipoatrophy and volume loss warrant future research, because this might prompt development of therapies

Figure 5. Grade 5 facial lipoatrophy.

that could actually reverse or prevent these processes, rather than mask their appearance.

Age and Lipoatrophy

As patients age, both genetic and environmental factors influence the skin and the tissues over which it lies. Balance is lost between bone, muscle, fat, and skin, as progressive changes occur in their volume, shape, position, and composition. By adding volume to certain areas, the shape and position of other structures can be altered, resulting in the reappearance of more youthful contours.

Causes of Age-Related Volume Loss

In general, although bones are maintained in early adulthood by remodeling processes, with age, less new bone is formed than resorbed, resulting in bone volume depletion.[25] The face does not escape this phenomenon, although there is some evidence indicating that the physiologic changes that occur in the mandible, for example, differ from those observed elsewhere in the body.[26] More superficial volume loss can also be explained by chronologically aged skin becoming more prone to perturbations of barrier function than younger skin, so less water is retained.[27–29] Also contributing to the flattening of facial contours with age is the reduction in collagen-I synthesis and acceleration of its degradation as a response to exposure to ultraviolet radiation.[30] In addition, collagen and elastic fibers are reorganized with age, with at least one histologic study suggesting that elastic fibers become arranged in a more tortuous manner, thus becoming distorted and less elastic over time.[31] Given the crucial role collagen-I and elastin play in providing cutaneous tensile strength and resiliency, their decline with age contributes to sagging and laxity. Gravity also exacerbates the appearance of skin, fat, and muscle laxity, as does the redistribution of fat, resulting in localized lipoatrophy and lipohypertrophy in the lower face and the neck of some patients.[15,18] For many patients, wrinkles form the focus of their facial rejuvenation, without addressing the contour changes that result from fat redistribution and other structural alterations. With this focus it is unlikely that they will appear much younger than their chronological age.

More research into the mechanisms controlling the processes described above could lead to advanced therapies. Manipulation of the genetic processes that underpin aging offers an exciting, if distant, prospect. Elucidation of the biochemical and cellular mechanism could eventually translate into more effective nonsurgical interventions, and greater understanding of the anatomy of aging could lead to more pleasing surgical rejuvenation techniques.

HIV and Lipoatrophy

There is little doubt that facial lipoatrophy is one of the most distressing signs of HIV infection. Not only is facial lipoatrophy aesthetically unattractive, but the reflection of the patient's face becomes a constant reminder of their diagnosis. Patients feel that their HIV status is unmasked by the appearance of facial lipoatrophy, leading to real or perceived stigmatization and discrimination.

Despite a large number of emerging theories, the mechanisms responsible for body fat and metabolic changes, and how the two interact, have not been firmly established. Protease inhibitors and nucleoside analogs are thought to inhibit adipocyte differentiation, alter mitochondrial function in adipocytes, and interfere with leptin, adiponectin, and cytokine expression in the adipose tissue of treated patients. Because adipose tissue itself is a metabolic organ, many links are proposed between lipodystrophy and the wider metabolic consequences of antiretroviral therapy.[32] Body fat and metabolic changes also occur in the absence of both protease inhibitors and nucleoside analogs and in the absence of therapy altogether. Indeed, individuals without HIV or disease also show peripheral lipoatrophy and/or central fat accumulation, albeit to a lesser degree.[33]

From this complex picture a clear need for greater research emerges. With greater understanding, new therapies could be developed to prevent or reverse lipodystrophy and lipoatrophy associated with

HIV or perhaps even reverse the fat changes that occur with age. Such research may also go some way towards curing genetic disorders, such as Dunnigan's, or even treat obesity.

Validation of the Developed Facial Lipoatrophy Grading System

The facial lipoatrophy grading system should be easily applicable and relevant to those physicians and patients for whom it was designed. Validation would credit the scale with scientific acceptability, encouraging the physician to apply the scale as the standard means of assessing facial lipoatrophy. In turn, this would facilitate ease of comparison and synthesis between data collected by different investigators. A study is proposed in which physicians would apply the facial lipoatrophy grading scale to independently assess the severity of lipoatrophy depicted in a number of patient photographs. The level of correlation between the assigned grades would be calculated and issues demanding further definition identified. One such issue likely to emerge is the way photographs of patients are taken, and for this reason, illustrations were used to depict the grading scale instead of photographs. Standardized means of taking photographs should be developed, whereby patients are assigned grades under similar conditions. Clearly the angle(s) at which photographs are taken, lighting conditions (direction and intensity), and facial expression(s) captured will impact the way lipoatrophy could be evaluated. Therefore, each should be controlled as much as possible.

Correlation of Refined Facial Lipoatrophy Grading System with Objective Measures of Facial Lipoatrophy

Because of the expense and technical expertise demanded, methods of quantifying lipoatrophy (such as ultrasound, MRI, CT scanning, and advanced topographic imaging techniques) are likely only to be used in the clinical trial setting. If relationships between the thickness of dermal layers and the subcutis could be correlated with the lipoatrophy grading scale, however, the scale could serve as a useful proxy measure of facial volume.

Validation and Correlation of Objective Techniques of Measuring Facial Lipoatrophy

There is no standard and accepted means of assessing facial lipoatrophy because each technique is associated with both advantages and disadvantages. As different investigators have used, and continue to use, different means to quantify facial soft tissue, validation and correlation of existing techniques would facilitate meaningful comparison between data gleaned from different studies. A new technique that offers promise in measuring the success of soft-tissue augmentation procedures is advanced photographic three-dimensional microtopography imaging (Primos, Canfield, Fairfield, NJ). This technology can detect minute elevation differences on the skin surface, which can be computer analyzed to reconstruct a precise three-dimensional profile of the skin surface.[34] Systems such as these are ideally suited to follow patients through the treatment process, as they provide an objective measurement of volume expansion. A major disadvantage of the technology, however, is that it does not measure epidermal, dermal, or fat volume, but rather topographic facial architecture. Although the use of microtopography imaging is in its infancy, it is gaining acceptance among U.S. dermatologists and plastic surgeons to assess wrinkle improvement. Research is required to validate this method for use in assessing volume loss and to compare results with those obtained by more established means, such as ultrasound.

The Panel has attempted to develop a simple, straightforward method of assessing facial lipoatrophy. We encourage the testing of this scale in individual practices and welcome feedback in its application.

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